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THE PARASYMPATHETIC INNERVATION OF THE LARGE INTESTINE IN THE HUMAN FETUS*

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Introduction

Both the vagus and pelvic splanchnic nerves (pelvic nerves, nervi erigentes) contribute to the parasympathetic innervation of the large intestine. Parasympathetic nerve fibers of vagal origin pass through the esophageal, coeliac, and superior mesenteric plexuses and then form small mesenteric nerves which accompany branches of the superior mesenteric artery to the proximal parts of the colon. Vagal branches are believed to supply the large intestine as far caudad as the middle or distal third of the transverse colon[1,2]. But the actual extent of the colon supplied by the vagus nerves in man is not definitely known. Data obtained in animal experiments on the vagal supply of the colon are controversial and may not be applicable to man.

Klee[3] believes that the vagi do not innervate the large bowel of most animals and Carlson[4] is convinced, from his physiological investigations, that these nerves are not distributed to the colon of the dog. On the other hand, Schmidt[5] found degenerated nerve fibers in both the ascending and traverse segments of the colon after cutting the vagi in this animal.

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Parasympathetic nerve fibers of sacral origin are components of the pelvic splanchnic nerves, which are branches of the anterior primary divisions of the 2nd, 3rd, and 4th sacral nerves in man. Most of the pelvic splanchnic nerve fascicles enter the pelvic plexus through which their nerve fibers are distributed to the erectile tissue of the genital organs, to all the pelvic viscera including the rectum, and to the sigmoid and descending portions of the colon.

Our knowledge of the sacral parasympathetic innervation of the large bowel in man is based primarily on gross studies. From dissections of adult human material, Mitchell[7], Telford and Stopford[8], Trumble[9], Lannon and Weller[10], and Woodburne[11] have described the course of parasympathetic nerves to the sigmoid and descending segments of the colon. These investigators demonstrated branches of the pelvic splanchnic nerves which pass rostrally in the hypogastric nerves (inferior hypogastric plexuses). The branches leave the hypogastric nerves caudal to the bifurcation of the hypogastric plexus and course through the sigmoid mesocolon and along the posterior abdominal wall to reach the sigmoid and descending portions of the colon. Telford and Stopford state that branches of the parasympathetic nerves to the descending colon accompany branches of the left colic artery. Wood-

burne, who dissected young, unembalmed specimens, found that none of the parasympathetic nerves which are distributed to the colon accompany arteries, except terminally where the nerves join the vasa rectae to enter the intestine.

In their gross dissections of human material none of the above mentioned investigators have been able to demonstrate sacral parasympathetic nerves extending rostral to the splenic flexure. Telford and Stopford, from results observed in patients with presacral neurectomies, are of the opinion that parasym-

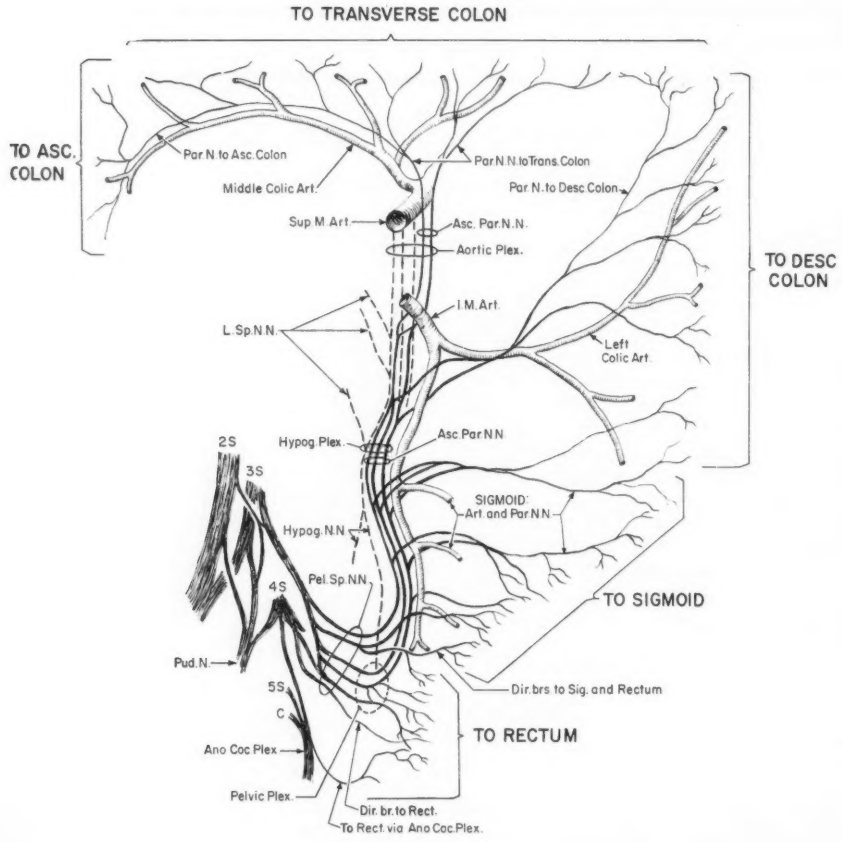

Fig. 1

A digrammatic reconstruction of the sacral parasympathetic nerve supply of the large intestine in a 64 mm human fetus. The pelvic splanchnic branches are illustrated on one side only. Note the relations of the ascending parasympathetic nerves to the inferior mesenteric artery, the hypogastric nerves and the hypogastric and aortic plexuses. Ano. Coc. Plex., Anococcygeal plexus; Asc. Par. N. N., Ascending parasympathetic nerves; Dir. brs. to Sig. and Rectum, Direct parasympathetic nerve branches to sigmoid colon and rectum; Dir. brs. to rectum, direct parasympathetic nerve branches to rectum; Hypog. N. N., hypogastric nerves; Hypog. Plex., hypogastric plexus (presacral nerve); L. Sp. N. N., Lumbar splanchnic nerves; I. M. Art., Inferior mesenteric artery; Par. N. to Asc. Colon, Parasympathetic nerve to ascending colon; Par. N. N. to Trans. Colon, Parasympathetic nerves to transverse colon; Pel. Sp. N. N., Pelvic splanchnic nerves; Pud. N., Pudendal nerve; Sigmoid: Art. and Par. N. N., Sigmoid arteries and parasympathetic nerves to the sigmoid; Sup. M. Art., Superior mesenteric artery; 2S, 3S, 4S, 5S and C, anterior primary divisions of 2-5 sacral and coccygeal spinal nerves.

pathetic fibers of sacral origin are not continued rostrally in the hypogastric plexus of man. Yet, Schmidt[5] showed that sacral parasympathetic nerve fibers of sacral origin are distributed to all parts of the colon in the dog, and Carlson[4] obtained muscular contractions in the ascending colon when he stimulated the pelvic splanchnic nerves in the same animal. Also, Langley and Anderson[12], Debaisieux[13], and others demonstrated experimentally that nerve fibers from the pelvic splanchnic nerves extend into the hypogastric plexuses in various animals.

Do parasympathetic nerve fibers of sacral origin supply the transverse and ascending segments of the colon in man? And if they do, what routes do the nerves follow to reach the rostral parts

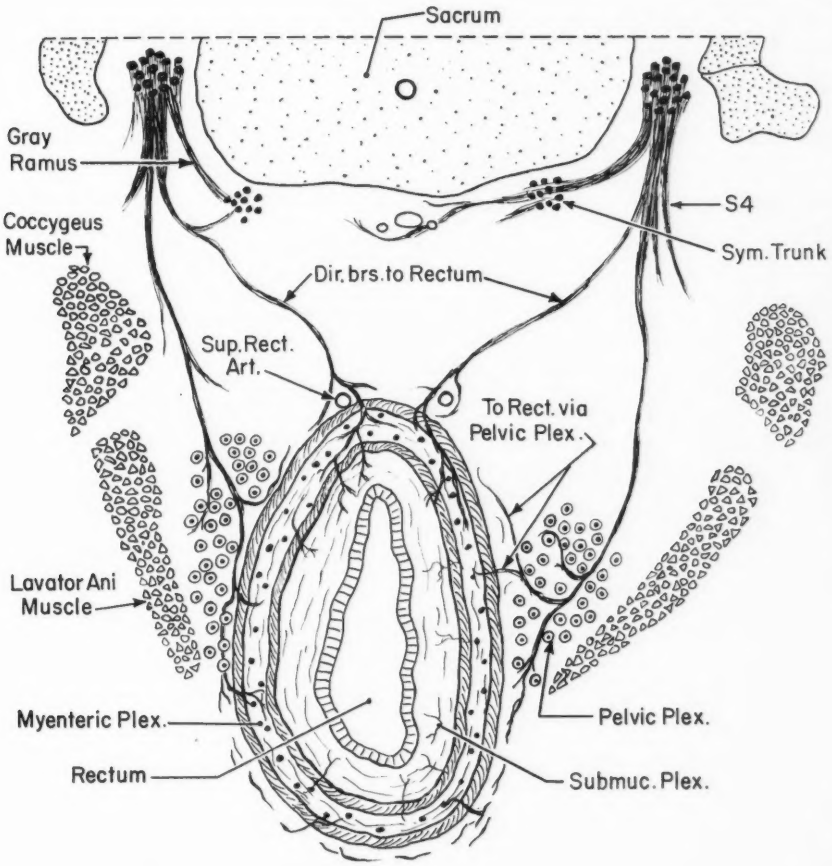

Fig. 2

A camera lucida drawing of an oblique section through the pelvis of a 46 mm human fetus at the level of the 4th sacral nerve. To show their continuity, the direct nerves to the rectum and the nerves to the rectum via the pelvic plexus have been reconstructed from several sections of the fetus. Note that the rectal branches enter the myenteric plexus posteriorly in the upper part of the rectum (which, because of the obliquity of the section, is higher in the illustration) and from any point on the rectal surface farther caudally. Dir. brs. to Rectum, Direct parasympathetic nerve branches to rectum; Submuc. Plex., Submucous nerve plexus; Sup. Rect. Art., Superior rectal (hemorrhoidal) artery; Sym. Trunk, sympathetic trunk and ganglion.

of the large bowel? In an attempt to answer these and other questions concerning the parasympathetic innervation of the large intestine, the distribution of the pelvic splanchnic nerve branches to the colon have been studied in human fetuses. A preliminary report of our results is presented below.

Material and Methods of Preparation

Eighteen human fetuses, ranging between 20 and 160 mm in Crown-Rump length were used in this investigation. The fetuses were sectioned in the frontal, saggital, and transverse planes and prepared either by the protargol or Holme's silver techniques.

Results

The parasympathetic innervation of the rectum. The parasympathetic nerve fibers distributed to the rectum are contained in pelvic splanchnic nerves derived from the anterior primary divisions of 3rd and 4th sacral nerves. Branches of the pelvic splanchnic nerves reach the rectum by three routes: via direct branches, via the pelvic plexus, and via the anococcygeal plexus[14].

The direct branches to the rectum arise from the sacral nerves as the latter exit from the anterior sacral foramina. Four to six direct branches are present on each side. They course medially along along the ventral surface of the sacrum and enter the rectum directly. They do not traverse the pelvic plexus nor do they accompany blood vessels (Figs. 1 and 2). The rostral filaments of the direct branches enter the rectum posteriorly while the caudal branches encircle the ampulla and penetrate its wall at any point on its surface (Fig. 2).

The parasympathetic nerve fibers reaching the rectum via the pelvic plexus are contained in pelvic splanchnic nerves with fibers distributed to other pelvic viscera. These pelvic splanchnic branches arise from the distal parts of the 3rd and 4th sacral nerves and enter the lateral aspect of the pelvic plexus (Fig. 2). Within the pelvic plexus, filaments pass dorsally and caudally to the rectum. The dorsally directed fasciles penetrate the posterior wall of the upper part of the rectum while the caudally coursing nerve bundles innervate the rectal ampulla and enter its wall at any point on its surface.

The nerve fibers reaching the rectum via the anococcygeal plexus are derived from the anterior primary division of the fourth sacral nerve. They pass caudally through the anococcygeal plexus and then form a small nerve which turns medioventrally around the anterior sacrococcygeus muscle to enter the dorsal wall of the ampulla (Fig. 1).

The nerves entering the rectum pierce its external muscle layer and join the myenteric plexus. From this plexus nerve fibers are distributed to the smooth muscle coats and to the submucosal plexus. In the anal canal, the myenteric plexus is supplemented by rectal branches from the pudendal nerve. The rectal branches pass between the deep and superficial external anal sphincter muscles and turn caudad within the myenteric plexus (Fig. 3). None of the nerve fibers of pudendal origin extend rostrally toward the ampulla. The rectal branches probably contain somatic afferent (general sensory) fibers which supply the mucosa in the caudal part of the anal canal.

The parasympathetic innervation of the sigmoid colon. The parasympathetic nerves supplying the sigmoid colon are diagrammatically illustrated in Fig. 1. They are derived from the 3rd and 4th sacral nerves and reach the sigmoid colon as direct branches of the pelvic splanchnic nerves and as branches of the ascending parasympathetic nerves.

The direct branches course medially, along the ventral surface of the sacrum and behind the pelvic plexus, to enter the sigmoid mesocolon through which they pass to reach the sigmoid colon. They do not accompany blood vessels except terminally, where they follow the vasa rectae of the sigmoid arteries into the gut wall.

The ascending parasympathetic nerve fibers of sacral origin are branches of the pelvic splanchnic nerves which extend rostrally into the abdomen to supply the colon and ureter (Fig. 1). In the caudal regions of the human fetus, the ascending parasympathetic nerves lie

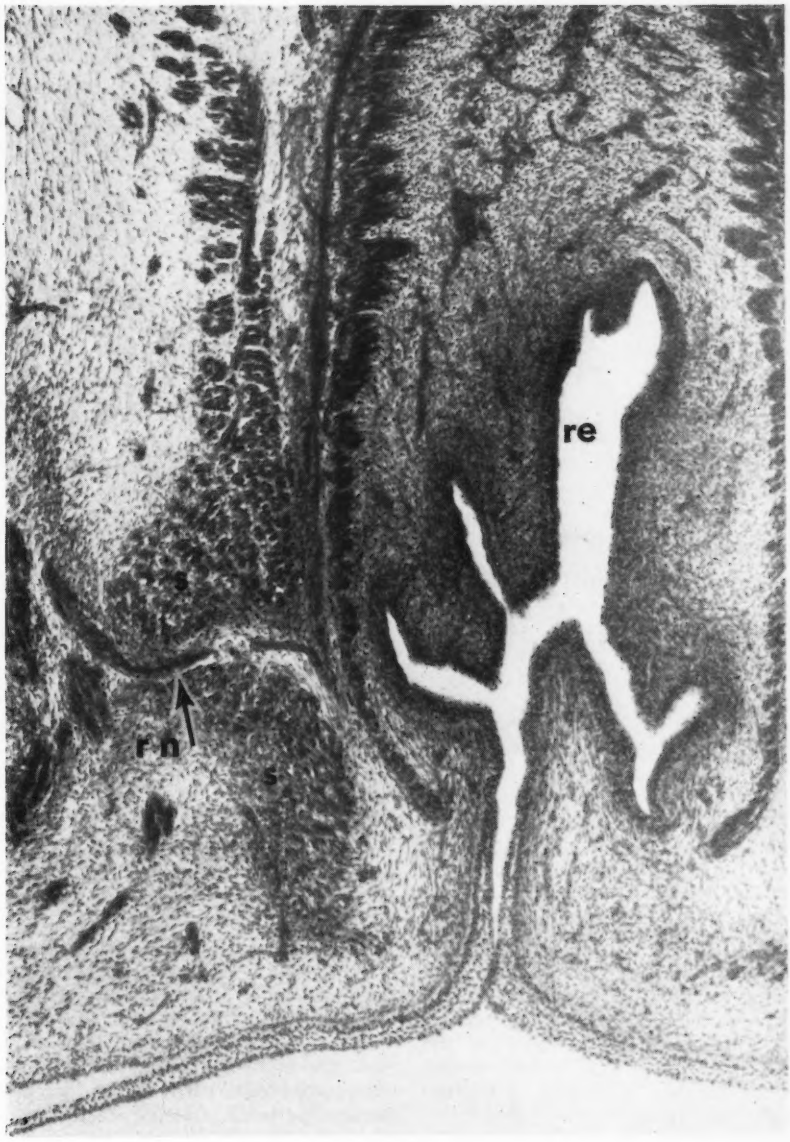

Fig. 3

A photomicrograph of a vertical section through the rectum and anal canal of a 46 mm human fetus showing rectal branches of the pudendal nerve entering the myenteric plexus. Note that the nerve fibers contributed to the myenteric plexus by the pudendal nerve are all distributed toward the anal orifice. re, rectum; r n, rectal branch of pudendal nerve; s and s, internal and external parts of the external anal sphincter muscle. Original magnification, x44, Holmes' silver.

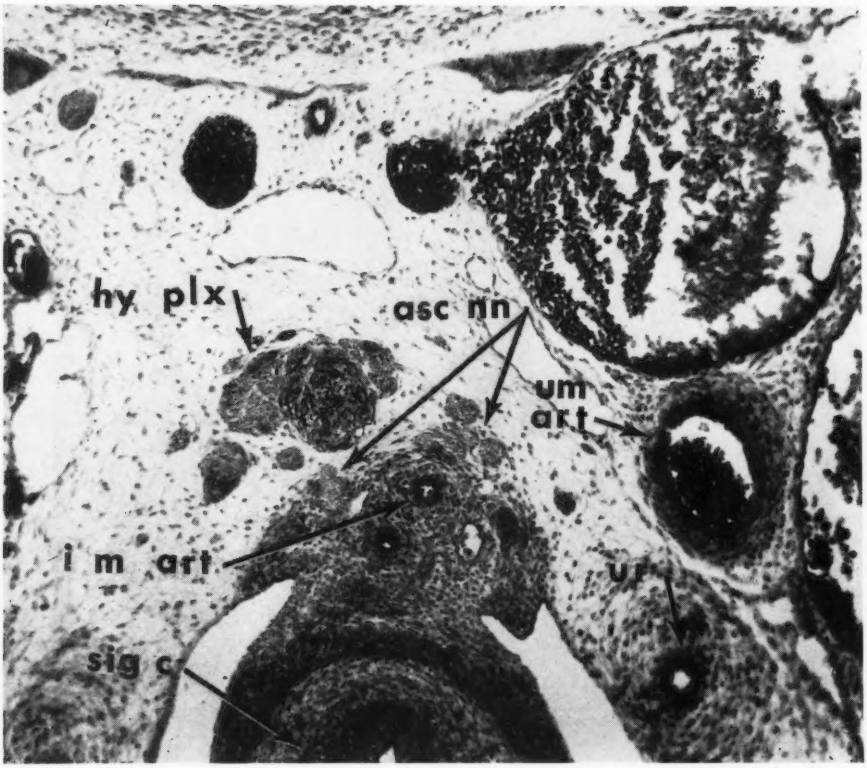

Fig. 4

A photomicrograph of a cross section through the caudal part of the sigmoid colon in a 33 mm human fetus to illustrate the relations of the ascending parasympathetic nerves (asc. nn.) to the hypogastric plexus (hy. plx.) and the inferior mesenteric artery (i. m. art.) um. art., umbilical artery; ur., ureter; sig. co., sigmoid colon. Original magnification, x60, Holmes' silver.

dorsolateral to the inferior mesenteric artery[15] and ventral to the hypogastric nerves (Fig. 4). Farther rostrally, the ascending parasympathetic fascicles lie in the ventral aspect of the hypogastric plexus (presacral nerve) and in the nerve fascicles of the aortic plexus which are located to the left of the abdominal aorta (Fig. 1).

In the pelvis, at the level of the hypogastric nerves, three or four parasympathetic branches arise from the ascending parasympathetic nerves to be distributed to the sigmoid colon. The sigmoid nerves originate as right and left branches which pass on either side of the inferior mesenteric artery to enter the mesocolon. In some fetuses the two branches join to form a single trunk after coursing around the artery. In others, they remain separate throught their extent to the sigmoid colon.

In the proximal part of their course through the mesocolon the nerves to the sigmoid which arise from the ascending parasympathetic fascicles accompany the sigmoid arteries. Distally, however, the nerves and arteries separate and follow independent routes until they reach the colon. Then the branches of the nerves and arteries converge and enter the gut wall together.

The parasympathetic innervation of the descending colon. The nerve supplying

parasympathetic fibers to the descending colon arises from the hypogastric plexus near the bifurcation of the aorta (Fig. 1). The nerve is formed by branches from the ascending parasympathetic nerves which, at this level, are located ventrally in both sides of the hypogastric plexus. The branches from the right and left sides converge toward the midline and then turn ventrally into the mesocolon. In some fetuses, the two branches remain separated, and take parallel courses throughout most of their extent in the mesocolon; in others, the two branches unite at the root of the mesocolon to form a single nerve trunk.

In the older fetuses, in which the gut has been retracted and has assumed its definitive position in the abdomen, the nerve to the descending colon ascends to the left and crosses the inferior mesenteric artery distal to the origin of its left colic branch (Fig. 1). The nerve accompanies the left colic artery for a short distance and then divides into branches which follow routes to the descending colon independent of those taken by the blood vessels. The terminal branches of the nerve, like those distributed to other parts of the colon, accompany vasa rectae into the intestinal wall. The branches of the nerve to the descending colon are distributed to the entire descending colon, to the splenic flexure, and to the left portion of the transverse colon.

The sacral parasympathetic innervation of the transverse colon. After contributing branches to the sigmoid and descending segments of the colon, the ascending parasympathetic nerves continue rostarally to supply the transverse colon. The ascending nerves pass through the hypogastric and aortic plexuses and enter the transverse mesocolon (Fig. 1). In some specimens, the nerves which ascend through the abdomen are closely applied to the left border of the aorta and constitute an integral part of the aortic plexus. In other fetuses, the ascending nerves are located slightly to the left of the aorta and accompany a small artery which interconnects the inferior mesenteric and inferior pancreatico-duodenal arteries.

In one of the fetuses, nerve fibers of sacral origin reach the transverse colon via a separate nerve. This nerve originates from the hypogastric plexus just caudal to the origin of the inferior mesenteric artery in a common trunk with the nerve to the descending colon. The trunk divides as it crosses the inferior mesenteric artery, and the aberrant branch to the traverse colon ascends along the left side of the posterior abdominal wall. In its course through the abdomen, this nerve lies on the ventral aspects of the left kidney and left suprarenal gland. Its distribution to the transverse colon is similar to that of the fascicles which ascend in the aortic plexus.

At the root of the transverse mesocolon, the ascending nerves to the transverse colon lie to the left of the superior mesenteric artery and its middle colic branch. As these nerves continue through the mesocolon, some of their branches join the middle colic nerve plexuses and are distributed with them to the right portion of the transverse colon and to the upper part of the ascending colon. The other branches of the nerves of sacral origin are distributed to the middle and left parts of the transverse colon. These branches can be followed as discrete fascicles through the mesocolon: they do not follow branches of the middle colic artery and they are interconnected with the periarterial sympathetic nerve plexuses only where they cross blood vessels. Terminally, the branches of the ascending nerves join the periarterial nerve plexuses and accompany the vasa rectae into the wall of the transverse colon.

Obviously, the function of nerve fibers cannot be determined from their microscopic appearance. However, we believe the ascending nerves distributed to the transverse colon are parasympathetic nerves of sacral origin. They are direct extensions of the ascending parasympathetic fascicles which are formed from branches of the pelvic splanchnic nerves and from which the parasympathetic nerves supplying the sigmoid and descending segments of the colon are derived. Moreover, their mode of distribution through the mesocolon is similar

to that of parasympathetic nerves supplying other segments of the colon. Parasympathetic nerves either follow routes completely different from those of blood vessels or, if they follow arteries, the nerves lie a short distance from the vessels they accompany.

Clinical Considerations of Sacral Parasympathetic Nerves

The pelvic splanchnic nerves contain sacral parasympathetic nerve fibers which supply the colon, urinary bladder and other pelvic viscera. These nerve fibers are excitatory to the detrusor muscle of the urinary bladder and inhibitory to its internal sphincter. Activation of the sacral parasympathetic nerves distributed to the bladder causes contraction of the smooth muscle in the bladder wall and relaxation of the internal urinary sphincter: the sacral parasympathetics are "bladder emptying" nerve fibers.

The sacral parasympathetic nerve fibers distributed to the colon are excitatory to its smooth muscle layers. When the parasympathetic nerve fibers supplying the colon are stimulated, increased peristalsis of the large bowel results and its contents are propelled toward the anal orifice. The colonic parasympathetic nerves are also probably essential in the regulation of secretion of the numerous mucous glands in the mucosa of the colon.

The pelvic splanchnic nerves very frequently are damaged during pelvic surgery. Trauma to these nerves results in the loss of urinary function and an impairment in the action of the large intestine, both of which persist until the neuronal reflex arcs are reestablished.

The parasympathetic nerves which ascend through the hypogastric and aortic plexuses, and their branches which course rostrally and laterally on the posterolateral abdominal wall are vulnerable during abdominal surgical procedures. The position of the pelvic splanchnic nerves in the pelvis and the routes followed by their branches through the pelvis and abdomen should be kept in mind during all operative procedures involving the pelvis and posterior abdominal wall. When feasible, dissection techniques should be used which permit the surgeon to visualize the parasympathetic nerves of sacral origin and great care should be taken to avoid damage to them.

Studies of the human embryo reveal that the entire colon may receive parasympathetic nerve fibers of sacral origin (Fig. 1). If these interpretations are correct, then an arrest in development of the pelvic splanchnic nerves, or of their postganglionic neurons, is responsible for congenital megacolon. The neurons constituting the intrinsic plexuses of the colon migrate along the preganglionic parasympathetic nerve fibers, in the embryo, to reach the gut wall. It is possible that an unequal distribution of preganglionic fibers to the colon, an abnormal distribution of postganglionic neurons within the wall of the colon or the failure of establishing a functional continuity between the pre- and postganglionic neural elements which supply a specific segment of the colon may be the precipitating cause of congenital megacolon.

Summary

1. Parasympathetic nerve fibers of sacral origin probably supply all segments of the large intestine in man. These nerve fibers are derived from the anterior primary divisions of the third and fourth sacral nerves and they are distributed to the large intestine through branches of the pelvic splanchnic nerves.

2. Branches of the pelvic splanchnic nerves are distributed directly to the rectum and anal canal. Other branches of these nerves reach the rectum via the pelvic and anococcygeal plexuses.

3. Rectal branches of the pudendal nerves join the myenteric plexus in the wall of the anal canal. These branches are distributed toward the anal orifice and most likely contain somatic afferent (general sensory) nerve fibers which supply the mucosa in the distal part of the anal canal.

4. Branches of the pelvic splanchnic nerves are also distributed directly to the caudal part of the sigmoid colon. Three to four additional parasympathetic branches reach the sigmoid colon via ascending fascicles in the hypogastric nerves.

5. The parasympathetic nerve supplying the descending colon is derived from the ascending fascicles of the hypogastric plexus near the level of the bifurcation of the aorta. The nerve crosses the inferior mesenteric artery distal to the origin of its left colic branch and then passes upward and to the left to reach all parts of the descending colon, the splenic flexure, and the left portion of the transverse colon.

6. The parasympathetic nerve bundles which ascend in the hypogastric complex continue rostrally in the hypogastric and aortic plexuses and pass through the transverse mesocolon to reach the transverse colon. These nerves probably contain parasympathetic nerve fibers of sacral origin. They are distributed to all parts of the transverse colon and to the rostral portion of the ascending colon.

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PARALYSIS OF BULBAR MUSCULATURE
"BULBAR PALSY"

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There is considerable confusion in the use of the terms "bulb" and "brain-stem." Some consider the "bulb" to be only the medulla oblongata, while others may include the pons and even the mesencephalon. "Brain-stem" may include all three structures or perhaps only the pons and medulla. The clinician considers bulbar palsy a picture of impairment of functions in the tongue pharynx and larynx, with or without disturbed function of the face and jaw muscles. Thus, in clinical terms "bulbar palsy" is generally understood to be dysfunction in the medulla and pons. This excludes the mesencephalon where the third and fourth cranial nuclei reside. However, sometimes these functions are impaired in diffuse brain-stem disease which affects the bulb as well as the mesencephalon. When the latter is affected alone the term "mid-brain" disease applies.

Anatomy

The motor nuclei giving origin to the nerve supply to the bulbar musculature come from three sources, all of which are derived from the ventral motor plate[1].

A. *Somatic Motor* comprising the hypoglossal, abducens trochlear and oculomotor nuclei. They are located near the mid-line and are similar to the somatic motor part of the ventral horn of the spinal cord.

B. *Branchial Motor*—comprising the special visceral efferent nuclei which supply the musculature derived from the branchial arch mesoderm—namely, spinal accessory, ambiguous, facial and the motor (masticatory) trigeminal nuclei. These nuclei have an intermediate ventrolateral position.

C. *Visceral Motor*—comprising the general visceral efferent nuclei which give rise to the cranial parasympathetic outflow. These include the dorsal motor muscles of the vagus, inferior salivatory nucleus, superior salivatory and "lacrimal" nuclei and the Edinger-Westphal nucleus.

We are most concerned with those structures innervated by the somatic and branchial motor nuclei. The hypoglossal nucleus innervates the tongue. The nucleus ambiguous innervates the soft palate, and larynx. The facial nucleus innervates the facial muscles and the motor trigeminal nucleus, the pterygoid and masseter muscles.

The bulbar musculature is not only responsive reflexly but is subjected to voluntary action and hence there is cortical representation. The corticobulbar fibers arise in the inferior part of the motor cortex and proceed ipsilaterally through the centrum semi-ovale, the genu of the internal capsule, the pes peduncularis of the mid-brain to the pons and medulla. At the appropriate level these fibers drift across the mid-line to terminate at the motor neurones with two important exceptions. The corticobulbar (supranuclear) fibers to the spinal accessory go to both sides but mostly ipsilateral. Those to the facial nuclei innervating the frontalis muscles and in part the orbicularis oculi are distributed bilaterally, whereas those to the nuclei innervating the lower face are only contralateral.

Patho-Physiology

The clinical pictures of bulbar palsy have much in common regardless of the etiology. Usually there is bilateral involvement of greater or lesser degree of the larynx, pharynx, palate and tongue with or without weakness of the masticators and facial muscles. There may be bulbar dysfunction as a result of unilateral disease. Generally there is weakness in speaking or swallowing. The voice may

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become nasal because of failure of the soft palate to close off the nasopharynx. For the same reason liquids may regurgitate through the nose with attempts to swallow. Swallowing may be impaired because of weakness of the pharyngeal muscles. The voice may become hoarse if one recurrent laryngeal nerve is damaged. If the vocal cords on both sides are defective there will be a weak voice with choking on swallowing because of failure of the larynx to be closed off from the pharynx. With defective function of the tongue and/or lips speech may be slurred or incomprehensible from articulatory failure. The jaw may hang open loosely when the masseters and pterygoids are weak. When the lips are paralyzed saliva drools out of the mouth or it can't be swallowed. A so-called "myopathic facies" may appear when the muscles of the face are paretic and lose their capacity to display emotion.

Differential Diagnosis

Paralysis of the bulbar musculature may result from a lesion anywhere in the neuromuscular apparatus serving these important functions. The anatomical localization can be described on several levels.

A. Upper Motor Neuron (supranuclear)
B. Lower Motor Neuron (intramedullary)
C. Cranial Nerve (extramedullary)
D. Myoneural Synapse
E. Muscle

Although all may produce similar disorders of function in some degree there are differences in symptoms and signs which serve to distinguish them from each other. Furthermore, important associated findings indicate the various levels.

A. **Upper Motor Neuron Lesions** (supranuclear)

These lesions damage the corticobulbar fibers producing the important syndrome of "pseudobulbar palsy." The jaw hangs opens and the face is immobile even to the inability to close the eyes. Saliva drools out of the mouth. The tongue does not atrophy or fasciculate and can only be protruded slightly if at all with voluntary effort. These muscles may move automatically in yawning or smiling. Speech may be understood if the cortex is not damaged but its production may be nil because of loss of voluntary function in the speech apparatus. The jaw and snout reflex are brisk. Spontaneous laughing and crying occur as a result of defective inhibition of subcortical emotional centers. Associated findings may include signs of upper motor neuron disease in the extremities and paralysis of gaze movements.

Pseudobulbar palsy is found when there have been *bilateral "strokes"* simultaneously or at widely separated intervals. A left sided stroke may have recovered imperfectly and years later a right sided stroke may destroy the important remaining corticobulbar fibers and pseudobulbar palsy appears. A severe lesion in the dominant hemisphere may by itself produce the picture. Such lesions often recover with good supportive care.

Other types of pathology can produce the syndrome. It develops slowly in various *demyelinating diseases.* Occasionally it can be seen in *multiple sclerosis. Infiltrating gliomas* spreading across the corpus callosum can damage the corticobulbar system. Such syndromes arising in the region of the mid-brain and pons may be difficult to diagnose. *Extramedullary tumors or aneurysyms* may compress the upper brain-stem and interrupt the descending upper motor neuron. Unless they produce associated disorders it may be impossible to differentiate them from supratentorial lesions.

Insufficiency of the vertebral-basilar artery system[2] may produce hemiplegia on one side which recovers, only to appear on the other side, and with it may come pseudobulbar palsy. The disorder may appear with a quadriplegia. The tegmentum of the mid-brain may be destroyed and with it the reticular activating system to produce akinetic mutism[3]. If the damage is extensive and involves the periacqueductal region and subthalmic structures prolonged coma may ensue. *Tumors* of the upper brain-stem particularly a glioma in the basis pontis can produce a slowly progressive quadriplegia and pseudo-bulbar palsy. Signs

of increased intracranial pressure are late if they occur at all. The diagnosis is often mistakenly made of some other degenerative disorder.

B. **Lower Motor Neuron Lesions** (intramedullary).

This is the syndrome of bulbar palsy which is produced by any type of destructive disease of the motor nuclei in the pons and medulla. The signs which distinguish lower from upper motor neuron disease are not always clear. In acute lesions there may be no difference. In chronic lesions the important features are fasciculation and atrophy of the tongue. With electromyography the facial and jaw muscles show fibrillation potentials and other signs indicative of denervation.

Two general groups of bulbar palsy bear differentiation—*acute and subacute or chronic.*

I. Acute Lesions

Inflammatory or Toxic

Acute bulbar poliomyelitis[4]— It occurs during the warm months. The prodomata of generalized infection and signs of acute meningeal irritation are present. Then with or without paralysis elsewhere in the body there appear abruptly nasal speech, difficulty in swallowing and phonation and/or paralysis of the face.

The cranial nuclei may be damaged on one or both sides. Usually all the paralytic phenomena appear in rapid succession. However, I have seen unilateral facial paralysis appear on two occasions 10 days after the nasal speech, and dysphagia and a bilateral facial paralysis appear 11 days after the other paralytic bulbar phenomena[5]. The spinal fluid will generally show pleocytosis and elevated protein but the diagnosis may even be made clinically in the absence of these changes.

Rabies—produces an "inclusion body" encephalitis with characteristic bulbar involvement. The incubation period is 30 to 70 days. Signs of hyperkinetic encephalitis are early. In a few days reflex spasms of the throat muscles develop. The jaws become clenched. Swallowing and breathing become difficult. Such spasms and excitement occur for a few days until the patient goes into coma and dies.

Other forms of encephalitis or polioencephalitis quite rarely involve the bulb specifically. They generally involve midbrain structures so that ocular paralyses occur.

Infectious or toxic neuronitis may involve the motor nuclei of the brain-stem. A form of the *Guillain-Barre* syndrome may be recognized in the acute or subacute appearance of bulbar signs with albumino-cytologic dissociation in the spinal fluid. This may be accompanied by signs of encephalitis, peripheral neuropathy or radiculopathy. In its most characteristic form only bilateral infranuclear paralysis of the face occurs but there may also be difficulty with swallowing, chewing and speech.

Diphtheric or post-diphtheric involvement of the nervous system is rare. The most common manifestation is unilateral or bilateral palatal weakness appearing 10 to 20 days after the throat infection. The intrinsic and extrinsic eye muscles may be involved. Polyneuropathy occurs with deep sensibility defect giving the picture of "pseudotabes". These are manifestations of the toxin damaging the axone and cell body. The spinal fluid may show a high protein content without pleocytosis so that reference is made to the Guillain-Barre syndrome due to diphtheria.

Tetanus— produces neuronal damage with a rather recognizable type of bulbar difficulty. About 5 to 25 days after an injury trismus of varying degrees appears. Involvement of the pharynx produces dysphagia and when the face is affected there is risus sardonicus. The spread to other muscles of the body and the tetanic convulsions serve to help in the diagnosis. Local tetanus of the bulbar musculature may occur when the infected wound is on the face, involving the facial, oculomotor, trigeminal and hypoglossal nerves.

Botulism—is rare. It produces a toxic neuritis with mild gastro-intestinal symptoms. Visual difficulties appear and are followed rapidly by deafness and impairment of speech and swallowing, with nasal regurgitation. The weakness

spreads to the extremities if the case progresses. The diagnosis is extremely difficult to make except in the presence of an outbreak in which several cases appear.

Vascular Lesions

These are acute episodes which may involve one or both sides of the bulb. They may be due to focal hemorrhages or much more frequently to focal areas of encephalomalacia secondary to occlusion of a small arteriosclerotic or otherwise diseased vessels in the brain stem which are part of the vertebral-basilar system. One of the better known syndromes is *thrombosis of the posterior-inferior cerebellar artery—the Wallenberg syndrome.* The retro-olivary area of the the medulla and part of the cerebellum are infarcted so that there is ipsilateral cerebellar dysfunction, vertigo from damage to the vestibular nucleus, ipsilateral paralysis of the soft palate and pharynx from damage to the vagus nucleus, ipsilateral Horner's syndrome ipsilateral loss of pain and temperature on the face from damage to the descending trigeminal nucleus and contralateral loss of pain and temperature on the body from damage to the ascending spino-thalamic tract. Other brain stem syndromes from small focal softening which affect the tongue, palate, pharynx and larynx can be recognized but they are much less frequent. Unilateral lesions occur in the pons or medulla which paralyse bulbar musculature ipsilaterally and produce contralateral hemiparesis or sensory disorders. These are due to occlusion of a unilateral vessel which has derived its blood supply from the vertebral-basilar system.

Complete or incomplete occlusions of the vertebral-basilar system occur[6]. Complete occlusion of the basilar artery is generally rapidly fatal. It comes on abruptly with quadriplegia and paralysis of the bulbar musculature. If the lesion is high enough to destroy the mid-brain tegmentum consciousness will be affected. I have seen one such patient live for a year in a coma following accidental electrocution which produced thrombosis of the basilar artery. Lower level lesions may permit retention of consciousness but no movement of any kind can be executed. Sensation may be preserved. Final and complete occlusion may be preceded for months or years by signs of intermittent or incomplete occlusion, a syndrome known as *insufficiency* of the vertebral-basilar system. There may be transient episodes of bulbar signs with or without long tract involvment such as hemiparesis or hemihypesthesia. The symptoms are referable to the medulla, pons, mid-brain and occipital lobes. Sometimes there may be only bulbar signs or transient hemiparesis. Involvement of one side in one attack and then on the other side in another attack suggests this syndrome. Common manifestations are dizziness, dysarthria, dysphagia, hemiparesis, somnolence and ataxia. The diagnosis can be established by vertebral arteriography. Recognition is important because anticoagulant therapy is very helpful in the stage of transient phenomena to prevent the complete and fatal occlusion[7].

II. Subacute and Chronic Lesions

These comprise two broad categories, *degenerative* and *non-degenerative.*

The *degenerative disorder* is the classical "bulbar palsy." It is part of a chronic abiotrophic neuronal disease which, if it attacks the bulb, is bulbar palsy; if it attacks the spinal cord it is progressive muscular atrophy; if the upper motor neuron is also attacked it is amyotrophic lateral sclerosis. Any chronic progressive disorder of the bulbar musculature which is accompanied by a similar disorder in the spinal musculature is easy to recognize as this entity. When the syndrome is present in the bulb alone it may be difficult to recognize. Characteristically it is bilateral with weakness and atrophy of the tongue with fibrillation, dysphagia and nasal slurring speech. As the condition progresses these symptoms become worse, the head drops; the face becomes paralyzed, swallowing and speaking become impossible. The patient dies from inanition and pulmonary infection. Sensory disorders are lacking. Occasionally it starts unilaterally, perhaps with paralysis of one vocal cord. Only progression of the illness makes the diagnosis apparent.

Multiple sclerosis may produce bulbar palsy when the brainstem is the site of pathology. A complicated syndrome of dysphagia, dysarthria, ataxia and pyramidal tract signs may appear. In the presence of remissions and exacerbations such apparent multiple foci suggest multiple sclerosis. Pathology elsewhere in the neuraxis is common. However, in a progressive syndrome of this type one must always be alert to intra- or extramedullary tumors.

The non-degenerative lesions may be intramedullary or extramedullary. The important intramedullary lesions are *neoplasms* and *syringobulbia*. Both may produce similar pictures. In syringobulbia the descending nucleus of the trigeminal is damaged with consequent loss of pain and temperature with the preservation of touch. The descending motor tracts might also be involved. The diagnosis is easily established when such symptoms are accompanied by signs of a similar process lower down in the spinal cord.

Intrapontine and intramedullary tumors. Gliomas or vascular tumors are not uncommon, especially in children[8]. They start with cranial nerve palsies and then invade ascending or descending tracts. Cerebellar involvement on one or both sides may occur. They may be mistakenly diagnosed multiple sclerosis. The investigation may be entirely normal except for the posterior displacement of the acqueduct and fourth ventricle on pneumoencephalography. Sometimes a definitive diagnosis of intramedullary neoplasm or syringobulbia is made only after direct visual examination in the search for a surgically removable extramedullary tumor.

The extramedullary lesions may compress the bulb. Aneurysms of the basilar or vertebral artery may cause slowly progressive compression which is confused with abiotrophic bulbar palsy. The occurrence of transient occlusive phenomena as described should alert one to the situation. Vertebral arteriography will establish the diagnosis[9].

The Arnold-Chari malformation[10] in which the cerebellar tonsils are retracted into the cervical canal to compress the medulla occasionally causes dysphagia and dysarthria. The characteristic x-ray appearance of platybasia, increased intracranial pressure and posterior fossa exploration establish the diagnosis. *Tumors* in the region of the bulb are not uncommon. The most frequent is the so-called "angle-tumor" in the *cerebello-pontine angle*. It is the acoustic neurinoma arising from the 8th nerve. It is nearly always a unilateral lesion which produces tinnitus, impairs hearing, weakens the face, and causes hypalgesia of the face with loss of corneal reflex. When it becomes large enough, pressure phenomena produce ipsilateral cerebellar signs along with a lower motor neuron lesion of the tongue, palate and pharynx on one or both sides. These tumors often erode the internal auditory meatus and produce increased intracranial pressure. Other tumors in this area include, *meningiomas, chordomas* and *chordoblastomas* arising from the remnants of the primitive notochord. If there are no x-ray changes in the adjacent bones they may be difficult to differentiate from intramedullary tumors and exploration may even be warranted for this purpose.

C. Cranial Nerve Lesions—Extramedullary

Inflammatory and toxic processes which affect the peripheral neuron have been described. Extramedullary inflammatory disease may produce lower motor neuron bulbar palsy by involving the cranial nerves in a plastic exudate. The signs of meningitis and decerebrate phenomena along with the spinal fluid should make the diagnosis clear. *Extradural suppuration* may involve several cranial nerves on one side such as may be seen in diabetics. The patient is acutely ill with sepsis and the unilateral disorder will help point in the proper direction. *Dural and extradural* invasion by tumors, from the nasopharynx or metastatic, usually from the breast or lung may infiltrate cranial nerves on one or both sides or choke off the nerves as they emerge from the foramina in the skull. *Tumors*, primary and secondary, in the region of the jugular foramen may involve the ninth, tenth, and eleventh cranial nerves without involvement of

the tongue. X-rays of the jugular foramen may be helpful. *Extracranial involvement* of the cranial nerves may produce symptoms of bulbar disease. These are frequently traumatic or secondary to invasion by metastatic or primary neoplasms involving glands in the neck. The unilateral distribution and the specific combination of involvement of any of the last four cranial nerves will help to localize the lesion. Sometimes thyroid tumors in the neck or mediastinum or pulmonary tumors may involve the recurrent laryngeal branch of the vagus and paralyze the vocal cord on that side.

D. **Myoneural Synapse Disorder—Myasthenia Gravis**

This disease may occur from infancy to the eighth decade. Bulbar signs may appear independently or in conjunction with weakness of the extremities or of the extra-ocular muscles[11]. Fatigue develops gradually and is relieved by rest. Performance is better in the morning than later in the day. Only mastication may be affected, or it may be so widespread as to give the typical "myopathic facies" with the drooping lids, flattened expressionless face, hanging jaw, nasal speech, dysarthria and dysphagia. There is no atrophy of the muscles except very late in the disease when loss of function may become irreversible in some cases and there may be permanent paralysis and atrophy in the shoulders, face or even extra-ocular muscles. The syndrome can come on abruptly in relation to infection and remit spontaneously. There may be an enlarged thymus shadow or associated hyperthyroidism. Myasthenia gravis must often be differentiated from psychoneurosis. The diagnosis is established by the abolition of disability within 20 or 30 minutes after the intramuscular injection of 1.5 mgm. of neostigmine methylsulfate with 1/100 grain of atropine[12]. Improvement will last for two or three hours. Tensilon (edrophonium)[13] may be used but is more difficult to evaluate since its beneficial effects wear off in one or two minutes. It is given intravenously in the following manner. One c.c. of a solution containing 10 mg. of Tensilon is drawn into a syringe. Only 0.2 c.c. (2 mg.) is injected and the patient observed for one minute. One minute later another 3 mg. is given and the remaining 5 mg. is given one minute after the second injection. The test may be discontinued whenever an effect is observed. This test is more valuable in differentiating between intoxication due to overdosage with esterase inhibitor drugs and the profound weakness produced by the disease itself. In the former the symptoms are aggravated and in the latter they are relieved. Since the drug's effect is brief, no danger exists that can't be overcome within a few minutes.

Treatment of myasthenia gravis is usually limited to neostigmine bromide, mestinon and mytelase. Sometimes large doses of potassium chloride are added. Dosages of all these must be established on an individual basis. The organic phosphate compounds have not achieved popularity because of their danger. Sometimes a thymoma can be radiated. In young women with short duration of the disease thymectomy may be considered[14].

E. **Muscular Diseases**

The bulbar musculature may be involved in a primary muscle disease which is rarely first manifested there but more frequently is part of a wide-spread process. Such extra-neural bulbar palsies are not uncommon[15].

Progressive muscular dystrophy is not difficult to recognize after it is well established. The onset is early with progressive weakness and wasting of the extremities, trunk and even face. It starts in the proximal muscles. Usually there is a familial history. The myocardium may be affected along with the skeletal muscles. Late in the disease there is paralysis of deglutition and dysarthria. Characteristic pathologic changes in the tongue, pharynx and palate with preservation of the brain stem neurons is consistent with a diagnosis of muscular dystrophy. The diagnosis can be established by biopsy from a skeletal muscle along with electromyography[16]. There is no known effective treatment. There is an entity of muscular dystrophy starting late in life to which has been attached the label "menopausal." Its behavior is somewhat like the congen-

ital form but much slower in development. Wasting lags behind weakness. The pharyngeal musculature may be involved. This latter clinical fact has caused this syndrome to be related to polymyositis rather than dystrophy.

Myotonia atrophica (myotonic dystrophy. Oppenheim's disease) is related to the muscular dystrophies in that the skeletal muscle goes through a similar but slower degenerative process. In addition there is a myotonic reaction to percussion, particularly in the thenar muscles and tongue. Baldness, testicular atrophy and cataract formation are common. Weakness of the bulbar musculature occurs, particularly nasal speech indicating involvement of the soft palate. The bulbar signs are rarely of sufficient intensity to become a problem of management. These cases present the same difficulties in therapy as do progressive muscular dystrophy in general.

Polymyositis[17] is presumably an inflammatory, acute toxic or allergic disease of muscle which may resemble muscular dystrophy. If it is associated with skin changes it is called dermatomyositis. It may be acute or chronic and occur at any age. Any or all muscles may be involved including the pharaynx and esophagus. Muscles are painful and may be edematous. It may be part of a wide spread collagen disease which also involves the viscera. It may be so acute that death occurs within a few days. In more chronic cases it can be confused with muscular dystrophy or with other progressive wasting muscular diseases which affect the bulb, notably progressive neuronal degeneration (true bulbar palsy). Remissions and exacerbations can occur in polymyositis which do not occur in the other conditions. It may be impossible to differentiate dystrophy from polymyositis on histopathological grounds alone. The clinical course, electromyography and the favorable response of polymyositis to cortisone and ACTH will be helpful deciding features.

Summary

Impairment of function of the bulbar musculaturue is easily recognized by the appearance of trouble with speaking, chewing, swallowing and facial expression.

The disorder may arise at any level, from the cortex down to the muscle itself. Each level has certain characteristic features in itself. The presence of various associated findings will help to localize the lesion.

The bulbar paralysis may be the result of a wide-spread neurologic or neuromuscular disorder of which it may be the first manifestation. Only awareness of the broad possibilities of the etiology will permit an accurate differential diagnosis and correct therapy.

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CONCEPTS OF MULTIPLE SCLEROSIS

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Throughout the years which have elapsed since Charcot first described multiple sclerosis as a disease entity and correlated its clinical picture with the pathological findings, little has been added to the histopathology of the disease. Multiple sclerosis is recognized today as one of the commonest among neurological maladies, but it still remains one of the most baffling disorders. The etiologic agent is unknown, clinical diagnostic procedures and tests have not proven worthy, the course of the disease is capricious, marked by remissions and relapses, and no cures have been reported.

Multiple sclerosis is a chronic disease involving the central nervous system, with implication mostly of the motor, cerebellar and sensory functions, and a tendency to remissions and exacerbations. Approximately 90% of the individuals who develop multiple sclerosis do so before the age of 45, thus the person is struck down during the zenith of usefulness. Reports of authentic multiple sclerosis in children have appeared, occasionally confirmed by necropsy. I have seen multiple sclerosis in three youthful patients, one as early as the twelfth year of life. This case survived until twenty-one years of age. Both sexes are affected about equally, with a slightly higher occurrence in women.

The prevalence rates of multiple sclerosis are not devoid of error because of the various methodological approaches. Limburg in 1950 reviewed the multiple sclerosis mortality statistics in the United States and Canada from 1939 to 1946; the rates per 100,000 population ranged from 0.9 in 1939 to 1.1 in 1945 with a drop to 1.0 in 1946. Studies were based on hospital admission figures, private practice cases, mortality figures, and determination of the number of patients within an area with assessment of this in terms of the population. Allowance has to be made for duplications, readmissions, erroneous diagnoses on death certificates and unconfirmed by autopsy, and in the matter of comparing international statistics, one has to take into account a large number of uncertified deaths in some countries.

World wide incidence is statistically highest in cold climates and low in the warmer sub-tropical or tropical latitudes. It has been suggested that chilling or some factor in a cold climate could alter blood coaguality which may cause venular thrombosis in the nervous system. I have advised many a private patient to seek a warm dry climate. These patients showed an improvement, but the therapeutic value of change of residence is difficult to evaluate because some patients who have never moved to a warmer climate have also had fewer remissions. In recent years epidemiological surveys have been made to determine more accurately the course of multiple sclerosis. Dean[1] reported that multiple sclerosis is extremely rare in the area of Capetown, South Africa. Allison and Millar[2] in surveying 700 cases of multiple sclerosis in Northern Ireland, and using the census figure of 1951, arrived at a prevalence rate of 7.9 per 10,000 for persons over 20 years of age. Sutherland[3] found an over-all prevalence rate of 5.5 per 10,000 in northern Scotland. In addition, both of these investigators noted a significant familial incidence in their surveys.

Kurland et al[4] reported higher mortality rates from multiple sclerosis in Canada and Northern United States than in the southern states. They concluded that "the data on geographic distribution indicate that an exogenous factor is probably of prime importance in the etiology of this clinical syndrome, but whether the presence of the occasional indigenous cases in the South indicates that one specific causative factor that may be responsible for the majority of the cases in the North is absent or merely less

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prevalent in the South is still a matter of speculation." In all of the epidemiological investigations, the variations in prevalence rates appeared to be due to geographic factors, and unrelated to season, occupational, social and racial groups.

A small but significant familial incidence in multiple sclerosis, as reported by some authors, has suggested a genetically determined predisposition. The role of heredity in multiple sclerosis however remains uncertain. Curtius[5] in a study of 3,124 near and distant relatives of 106 cases of multiple sclerosis observed in Bonn and Heidelberg found a familial incidence in 9.4%. Pratt et al[6] reported a familial incidence of 6.5% in 310 cases. Mackay[7] critically reviewed the literature and added five of his own cases. A total of 84 family groups and 188 persons were reviewed which led him to conclude that the available evidence strongly suggests that multiple sclerosis exhibits a familial incidence more frequently than mere chance would determine. He theorized that (a) there is a familial, constitutional vulnerability to multiple sclerosis; this vulnerability, possibly non-essential and non-specific, is subclinical and, per se, inadequate to produce the disease; (b) there is a second, non-familial, possibly exogenous cause or group of causes which are competent to evoke the disease, especially when the first, or constitutional factor, is already present. Allison and Millar[2] traced 700 cases of multiple sclerosis; in 44 families they found more than one member affected, giving a familial incidence of 6.58%. These authors, too, believe that both genetic and environmental factors should be given consideration in the etiology of multiple sclerosis.

Some psychiatrists have suggested that multiple sclerosis appears in individuals with certain personality structures. Langworthy[41], from his personal experiences, concluded that these individuals are poorly adjusted emotionally before the symptoms of organic disease develop. He found that "these patients are emotionally immature and show this immaturity in all their interpersonal relationships. It is often evident in their sexual adjustment, which can be evaluated at a preadolescent level of emotional growth. The diagnosis of conversion hysteria is frequently made at the onset of the symptom, not alone because of the bizarre nature of the complaints but especially because of a personality structure consistent with this diagnosis. Later, when objective signs of organic cerebral damage appear, the diagnosis is abruptly changed to multiple sclerosis. It is probable that these patients have a tendency to conversion symptoms as well as showing the changes typical of multiple sclerosis. Conversion symptoms have been observed developing long after the organic signs of multiple sclerosis are apparent. Many patients are also aware themselves that periods of emotional turmoil tend to bring on new disabilities characteristic of the disease." Grinker et al[42] in a study of 26 cases of multiple sclerosis led them to believe that these patients were severely frustrated due to an excessive need for love and affection which was ungratified in childhood. My personal experience with cases of multiple sclerosis does not support the theory that there is a specific premorbid personality type. It is more likely that the emotional disturbances antedating the onset or relapse of the disease are caused by the frontal plaques.

A casual connection between pregnancy and multiple sclerosis is difficult to establish, although pregnancy usually exacerbates the symptoms.

Until recently the search for an etiologic agent in multiple sclerosis was focused on a single factor, but now it is believed by many investigators that the causation may be multi-factoral. Kurland suggested that two or more disease entities display the **multiple sclerosis syndrome** and the etiology may be different in northern and southern climates. A multitude of theories as to the possible etiology of this disease have been postulated, but only the more significant ones will be touched upon in this paper.

Infection. Viral and bacterial causes have been concerned with metatuberculosis, brucellosis, spirochetes, and virus

infection. Buzzard[9] in 1911 first proposed that the disease was due to an organism of the Treponema family, although he was not successful in demonstrating the organism. In 1952 and 1954 Steiner[10] reported on spirochaeta myelophthora found in the central nervous system of patients who had died of multiple sclerosis. He noted that in multiple sclerosis the spirochetes are located only in extracellular regions of the cerebral and spinal cord tissues and that the process of individual growth and reproduction does not involve any intracellular phase and is exclusively extracellular. Quoting Steiner:

> "The parallelism between the clinical manifestations, inflammatory reactions and their locations in regard to the presence of the spirochaeta myelophthora in acute lesions certainly indicates the pathogenic significance of these spirochetes. Our finding of extracellular granules is leading to the disclosure of intact spirochetes especially by using serial sections through entire tissue blocks. The heterophasic nature of the disease process should be emphasized. However, it is characterized by the presence of histologically old, more recent and fresh plaques; the variation of inflammatory reactions in relation to the stage of the plaque and the number of well preserved spirochetes and extracellular spirochetal granular debris in or near acute plaques is impressive . . .
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> "It is certainly premature to speculate about effects of exotoxins, endotoxins, or other chemical noxious substances derived from the spirochetes. Mechanical injuries to the tissues by these rapidly self-movable micro-organisms have to be considered also. There is finally a possibility that an indirect stimulation of neurological cells, such as astrocytes or microglial cells or even oligodendroglial cells (Lumsdan) by these micro-organisms may take place as a result of which these cells develop a myelolytic activity."

Ichelson[11] in 1957 devised a new culture medium in which it was possible to grow spirochaetes from spinal fluids of cases of multiple sclerosis; they were found to be identical in appearance to those found in the brain tissue by Steiner. This finding has not as yet been confirmed by others.

Allergy. Glanzmann[12] in 1927 suggested the allergic theory in the causation of diseases of the nervous system based on observations of post-vaccinal encephalitis. The theory of neuroallergy as a common basis in all of the demyelinating diseases, including multiple sclerosis, was further developed by van Bogaert[13], Pette[14], Ferraro[15], Lumsden[16], and others. Renewed interest in this theory followed reports of successfully induced allergic encephalomyelitis and demyelination (since these lesions most closely resemble multiple sclerosis) in different animals by intramuscular and subcutaneous injections of brain tissue together with an adjuvant mixture which is known to enhance antibody formation. These various experiments in the production of encephalomyelitis led to the theory of antigen-antibody reaction and that the brain tissue may contain a chemical agent which acts as an antigen producing antibodies that react with constituents of white matter. Allergy may be a clue in explaining the transitory nature of the symptoms and that the exacerbation of symptoms are due to exposure to specific allergens and the remissions due to lack of contact with such allergens. However, I believe that the transitory nature of the disease can also be explained on the basis of tissue inflammation which can be on an infectious basis, giving pressure on the nerves but not causing permanent damage to these nerves, thereby causing only transitory nervous system changes. The antigen-antibody reaction does not explain the production of similar demyelinating lesions, resembling those of multiple sclerosis, in nonallergic mechanisms. Demyelination in animals has been produced by injection of lipolytic enzyme[17, 18], cobra venom[19], the alpha toxin of Clostridium welchii[19], agents producing anoxia[20, 21], poisoning with carbon monoxide, nitrous oxide, and barbiturates[22].

To implicate allergy, Cooke[23] sets forth the following criteria: (1) an allergic con-

stitution; (2) a repeated history of symptoms; (3) a history of unusual or excessive contact with an allergen; (4) positive skin reactions, which if not specific as in other atopic diseases, at least indicate the allergic constitution of the patient; (5) elimination of a suspected allergen, if extrinsic, should relieve the symptoms, and that deliberate reintroduction of the suspected antigen should reproduce them.

Prigal[34] in a critical survey of the literature on the relationship of allergy to multiple sclerosis stated that the fifth criterion of Cooke may not hold in a disease entity in which allergy is not the sole factor but is associated with one or more agents acting simultaneously, or in which the allergen is intrinsic and cannot be eradicated. He further said, "Were this fifth criterion to be demonstrated conclusively in multiple sclerosis (and this has not occurred under controlled conditions), the case for an allergic role would be markedly enhanced and the search for specific allergens thereby intensified. It is significant that, with all the years of observation of patients by competent investigators, no report has completely fulled these criteria."

In the light of experiments that demyelination can be produced by both antigen-antibody reactions and nonspecific tissue response to many non-allergic agents, Prigal is inclined to favor Kurland's suggestion that multiple sclerosis may be a syndrome rather than a specific disease entity, and demyelination is only one of the signs, the extent of which (or even its presence) may vary from case to case. He believes that an allergic mechanism is apparently involved in the experimental production of encephalomyelitis, but the antigen, not yet specifically identified, is intimately associated with myelin tissue. He states further, "There is no complete correlation between experimentally induced encephalomyelitis and multiple sclerosis, which it resembles. Presumably, they both may be mediated through an allergic mechanism. In experimental encephalomyelitis the allergen is ordinarily extrinsic and is introduced by injection. In multiple sclerosis the mechanism remains obscure. Some evidence suggests autosensitivity, implying the release of a latent intrinsic allergen from brain tissue. . . . The development of specific tissue sensitivity (autosensitivity) as an explanation for multiple sclerosis has been considered. No mechanism for the clinical development of such an autosensitivity has been elucidated, however. Infection (viral and bacterial) has been suggested as a factor in the liberation of the antigen from nervous tissue and the induction of autosensitivity which is self-perpetuating. Possibly, cerebral allergy, due to an extrinsic cause, may initiate a similar mechanism."

The question arises as to the pathologic evidence to support the allergic theory. The majority of allergic disorders are kinetic and completely reversible with no pathologic evidence. However, the characteristic pathologic lesion of multiple sclerosis are widely scattered, discrete lesions in various parts of the central nervous system which appear to be irreversible.

Metabolic Disturbances. Many investigators have theorized that a fundamental biochemical derangement and alterations in cellular metabolism are responsible for multiple sclerosis. Brickner[25] reported abnormal lipolytic activity in the blood of multiple sclerosis patients; Weil and Bradburne[26] found low serum inorganic phosphorus, and related it to a disturbed phospholipid metabolism. Jones et al[27] concentrated on carbohydrate metabolism, and their studies suggested an abnormal metabolic pattern in the metabolism of carbohydrate, in which there is a partial block at the pyruvic acid level. A high blood pyruvic acid/lactic acid, low serum inorganic phosphorus with increased excretion of phosphorus after glucose, and elevated serum cholesterol has been helpful to them in establishing diagnosis of multiple sclerosis.

Circulatory Disturbances. Scheinker[30] undertook to determine the nature of the earliest stage of the pathologic process which might clarify the mechanism of plaque formation prior to scar formation.

He found that about two thirds of all the initial small lesions were found in close proximity to small veins which were extremely distended and showed signs of stasis and congestion. Only some of the veins were extremely distended and showed signs of stasis and congestion. Some were occluded by small thrombi composed of fibrin threads and large masses of agglutinated platelets. He concluded that multiple sclerosis lesions develop as the result of recurrent episodes of focal disturbance of nutrition by vasoparalytic vascular phenomena of the central nervous system which may result in prolonged stasis and "sludging of blood". This in turn may produce thrombotic occlusion of the small blood vessels and thus, through permanent impairment of the blood supply, give rise to circumscribed patches of demyelination. Further, this vascular phenomenon may explain the remissions and exacerbations which characterize the disease.

SYMPTOMS AND DIAGNOSIS

Today the majority of practitioners are familiar with the characteristic symptoms of the disease, but because of the unpredictability of its course, a precise definition of the pattern still cannot be formulated. Unfortunately, diagnosis is usually not confirmed until the 4th or 5th year of the disease when it is in a fairly advanced stage, and coarse intention tremors, nystagmus, and optic atrophy are already present. Close questioning of the patient will disclose that more or less indefinite symptoms had appeared quite some time previously, and it is the recurrence of these symptoms which make the patient seek medical advice. The precipitating factors have included fatigue and lassitude over a period of days or weeks, overwork, emotional stress, trauma, or infection such as sore throat, cold or influenza.

The most common initial symptom complained of is "weakness in the legs", or paresthesia, such as tingling, numbness, coldness, or burning. There may be vague pains in the back of limbs, or awkwardness in the use of a limb or fingers.

Ocular symptoms, such as transient diplopia or retrobulbar neuritis may be present. In the author's experience 22 per cent of the cases had bitemporal pallor due to atrophy of the optic nerve. There may be dissociation of eye movements or nystagmus.

The clinical picture depends on the site of nervous-system involvement. Lesions of the motor-pyramidal tract cause weakness, stiffness, and easy fatigability early in the disease. When the corticobulbar-spinal tract is involved, neurologically there is absence of normal reflexes, and hyperactive deep and pathological reflexes are present. Plaques in the cerebellar spinal tract are responsible for incoordination, staggering gait, intention tremors, scanning speech, and dysdiadochokinesia. When the brain is involved, the individual may have convulsions and even vomiting, but this is uncommon. Other symptoms presenting themselves may be bladder and rectal dysfunctions, vertigo, emotional imbalance, euphoria, and frequent crying spells. True urinary incontinence indicates severe sacral cord involvement.

The course of the disease is characterized by remissions and exacerbations and then again its course may be marked by insidious, gradual developing disabilities, without remissions, but with progressive gait impairment. The disease may also be of an explosive character with acute onset of illness, involving paralysis of limbs, speech and bladder difficulties, blindness, and mental clouding. As McAlpine[28] said, "One of the characteristic and at the same time puzzling features of multiple sclerosis is the extreme variability in the mode of onset and duration of the first symptoms. At one end of the scale is the so-called apoplectiform onset recognized by Charcot; at the other end is the slow insidious appearance of a paraplegia due to spinal plaques. How to explain these two modes of onset on the basis of a common pathological process is one of the many unanswered questions relating to this disease."

There is no simple diagnostic test available. Diagnosis of multiple sclerosis can only be arrived at when these signs

and dysfunctions are interpreted in terms of the site of the lesion in the central nervous system. Schumacher[20] stated that diagnosis of multiple sclerosis can be made on (a) clinical evidence indicating widely scattered, discrete lesions in various parts of the central nervous system and (b) a tendency for alleviation or remission of symptoms followed by recurrence.

Studies of the spinal fluid for proteins, and gamma globulin have been made and though there may be demonstrated an elevation of gamma globulin or increase in proteins[31, 32], as well as changes in the colloidal gold test, the findings are not pathognomonic of the disease because other neurological disorders show increased blood gamma globulin. Yahr et al[32] in 681 cerebrospinal fluid gamma globulin determinations found an elevation in 66.5% of patients having multiple sclerosis, 74% of the patients having neurosyphilis and in 6% of the patients having other diseases of the central nervous system. No relationship existed between the type of onset, course, duration or occurrence of new symptoms in multiple sclerosis and the elevation in cerebrospinal fluid gamma globulin. The highest incidence of elevated cerebrospinal fluid gamma globulin occurred in the cases of multiple sclerosis who had multiple attacks, multiple lesions and marked functional disability.

PATHOLOGY

The disease is characterized by an irregular, scattered distribution of plaques of demyelination throughout the white matter of the central nervous system, particularly in the brain stem, spinal cord and cerebrum, and in many cases there is demyelination of optic nerves causing the retrobulbar neuritis and impairment of visual fields. The pathologic findings vary and probably are due to the duration and severity of the disease, and whether the disease was acute or chronic. The acute form shows more p e r i v a s c u l a r infiltration and in the chronic form there is more scarring and involvement of the axis cylinders. Within the cerebral hemispheres the plaques are usually located in the white matter adjacent to the lateral ventricles, particularly near the anterior and posterior horns. Gray matter is sometimes slightly involved.

The earliest lesions show little edema of the myelin with some tissue damage. It is in this stage that the lesion is reversible since the axis cylinders of the fiber tracts are uninvolved. The transient nature of the disease can be explained patho-physiologically on the basis of the swelling of the myelin sheaths, which may be temporary and later may subside. With the progression of the lesion, there is a breakdown of myelin sheaths, cellular reaction, fatty phagocytosis, proliferation of gitter cells, infiltration of the perivascular areas with lymphocytes, and destruction of the axon cylinders. The irreversible scar then develops.

TREATMENT

A nihilistic attitude has existed in the treatment of this disease because the cases however treated still have a poor prognosis and a significant degree of disability is inevitable. Spontaneous remissions do occur. The effectiveness of any therapeutic agent in a disease with an erratic course such as multiple sclerosis is only significant if lasting remissions are induced and further progression of the disease is prevented. Too often a remission will occur and the treatment given during that period is credited for the improvement. In the absence of any specific therapy, the treatment of multiple sclerosis is a matter of general care.

Treatment has been directed to:

1. **G e n e r a l hygienic and supportive measures.** Adequate bed rest, physiotherapy, massage, occupational therapy and advice to the patient to move to a warmer climate and to avoid chilling and pregnancies.

2. **Preventive.** This therapy is aimed at preventing development of lesions in the nervous system and a multitude of measures may be utilized, such as the anticoagulants, vasodilators, histamine, circulatory stimulants, Vitamin E and Vitamin B_{12}, and liver extract.

Scheinker's management[30] of multiple sclerosis is based upon his vascular theory of the pathogenesis of the disease;

he aims at elevation of blood pressure and stimulation of the general blood circulation by vasopressor drugs as a counteraction to vasoparlytic vascular phenomena leading to stasis, sludging, and eventual thrombosis of the small blood vessels. Of 237 patients treated for periods ranging from 1 to 4 years, 157 (66.3%) showed either complete or partial recovery with respect to both subjective and objective signs of improvement; 57 (24.05%) improved only slightly and without evidence of neurologic changes; and 24 cases were complete failures.

3. **Symptomatic Treatment.** Almost every conceivable drug has been employed: sodium cacodylate, novarsenobillon, silver salvarsan, sodium salicylate, quinine hydrochloride, compound nucleo-proteid tablets, fibrolysin, curare, mephenesen. The value of ACTH and cortisone is questionable in the treatment of multiple sclerosis. Merritt et al[38] reported negative results with corticotropin and cortisone which seemed to be in agreement with other investigators. However, Alexander et al[40] in treating 554 patients with multiple sclerosis found that the only treatment showing an objective quantitative effect on the course of the illness was repeated blood transfusions and corticotropin (ACTH) therapy. On the other hand, they found that vitamin therapy, with the added use of muscle adenylic acid, had no measurable effect on the course of the disease in 170 patients as compared to its effect in 170 matched control patients who did not receive muscle adenylic acid. Their experience is contrary to that of Shapiro[39] who utilized muscle adenylic acid therapy and water-soluble vitamins in 26 patients for 367 patient-months and the results, although inconclusive, were encouraging. He employed this treatment on the assumption that one or more specific disturbances in intracellular metabolism play an important role in the pathogenesis of the disease, and that if the assumption that coenzyme A seems to be the most likely substance involved in the synthesis and breakdown of lipids, there may be a very significant connection between the therapeutic response of multiple sclerosis patients and the changes in blood plasma cholesterol which occur under intensive muscle adenylic acid therapy. The most convincing therapeutic observation in his study was the infrequency of true relapse in patients under muscle adenylic acid therapy.

Kurtzke and Berlin[33] reported 90% improvement of varying degrees in 30 patients treated with isoniazid. Tschabitscher et al[34] also obtained favorable results, but the results were negative in the cases of Hinterbuchner et al[35] and Dekaban[36]. In 1957 a Veterans Administrative Cooperative Study[37] conducted a rigid control featuring randomization of therapy and control of observational error and studied 186 patients (98 receiving a placebo and 88 isoniazid). The isoniazid had no beneficial effect on the course of multiple sclerosis during the 9 months or more of follow-up.

4. **Psychotherapy.** The physical symptoms cannot be controlled by psychotherapy but the patient's depressive periods, a natural concomitant of a disabling disease, can be alleviated. Physical therapy and physical rehabilitation enable the patient to resume some of his activities during the remission periods, and by undergoing such treatment the patient approaches his physical disability realistically. His anxiety can be relieved by the physician's sympathetic understanding in listening to the patient's feeling about this illness, and attempting to guide him in adjustments.

SUMMARY

Some of the more significant concepts on the etiology of multiple sclerosis have been presented, but the primary causation of the demyelintion is still unknown. Clinical evidence and pathologic studies have not yielded valid arguments that the disease is due to a virus or bacteria, or is based on some allergic mechanism, or biochemical disturbance with alterations in cellular metabolism. The available therapeutic measures have ameliorated the course of the disease only at times, and no definitive therapy is available because the cause of the disease remains obscure.

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CEREBRAL VASCULAR DISEASE

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The problem of cerebrovascular disease not only concerns the neurologist and neurosurgeon but almost everyone in the field of medicine, especially the general practitioner, internist, psychiatrist, pediatrician, geriatrician, surgeon and recently the radiologist with the increasing use of angiography. It is the third ranking killer and one of the foremost cripplers in the U.S.[1]

The scope of this article is not to present a complete review of all the aspects of cerebrovascular disease but (1) to clarify certain aspects which are vague in medical students' minds as to anatomy of the vascular supply of the brain and the resultant symptomatology due to involvement of these vessels, (2) to discuss the diagnosis of some of the more important cerebrovascular diseases because of the advances in therapy, and (3) to present the new classification of cerebrovascular disease which is not only important for academic reasons but again necessary because of the recent advances in therapy.

In June 1955 the National Advisory Council of the National Institute of Neurological Diseases recommended a new diagnostic classification be made and to eliminate the term cerebral vascular accident (C.V.A. as it is commonly abbreviated). The term accident connotates a blow or some other external traumatic event in the usual sense of the word. The term cerebrovascular disease was substituted. The classification is divided into 9 diagnostic categories and several subclasses. The classification is as follows:

I. Cerebral Infarction
   - A. Thrombosis and Atherosclerosis
   - B. Cerebral Embolism
     1. cardiac origin
     2. other than cardiac origin
   - C. Other conditions causing Cerebral Infarction
   - D. Cerebral Infarction of undetermined cause

II. Transient Cerebral Ischemia without Infarction
   - A. Recurrent focal cerebral ischemic attacks (previously called vasospasm)
   - B. Systemic hypotension (simple faint, acute blood loss, etc.)
   - C. Migraine

III. Intracranial Hemorrhage
   - A. Hypertensive
   - B. Ruptured Saccular Aneurysm
   - C. Angioma (ruptured)
   - D. Trauma
   - E. Hemorrhagic Disorders (leukemia, aplastic anemia, etc.)
   - F. Of Undetermined Origin
   - G. Hemorrhage into Brain Tumors

IV. Vascular Malformations and Developmental Abnormalities
   - A. Aneurysms
   - B. Angiomas
   - C. Absence, hypoplasia or other abnormalities of vessels

V. Inflammatory Diseases of Arteries
   - A. Infections and Infestations (meningo-vascular lues, tuberculosis, etc.)
   - B. Diseases of Undetermined Origin (lupus erythematosis, polyarteritis nodosa)

VI. Vascular Diseases without Changes in the Brain
   - A. Atherosclerosis
   - B. Hypertensive Arteries and Arteriolosclerosis

VII. Hypertensive Encephalopathy
   - A. Malignant Hypertension
   - B. Acute Glomerulonephritis
   - C. Eclampsia

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VIII. Dural Sinus and Cerebral Venous Thrombosis

A. Secondary to Infection of Ear, Nasal Sinuses
B. With Meningitis and Subdural Abscess
C. Debilitating States
D. Postpartum
E. Postoperative

IX. Strokes of Undetermined Origin

Copies of the complete classification can be obtained from the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

In order to fully comprehend the symptomology that occurs in vascular diseases of the brain it can be divided into 3 separate aspects:

1. The basic pathologic process which involves the vessel.
   a. Atherosclerosis
   b. Embolism
   c. Hypertensive Changes
   d. Malformations
   e. Spasms
   f. Arteritis
   g. Increased permeability to plasma and for cells.
2. The pathological and physiological changes in the cerebral tissue due to occlusion of the vessel (infarction or mixture of the vessel (hemorrhage).
3. The neurologic disturbance which results.

Brain tissue stores no oxygen and when it is deprived for more than a few minutes the cells are irreversibly injured. This, however, is modified by recent work on hypothermia[2]. The cells, both nerve and glial disappear, nerve fibers degenerate and the supporting tissue and smaller blood vessels are destroyed; the involved tissue becomes swollen and then disintegrates — a process called "softening". Over a period of time, the debris is removed and then fibroblastic and astrocytic connective tissue proliferates and forms a meshwork and knits the defect. This process is called infarction and the lesion an infarct.

The neurological picture depends primarily on which vessel is occluded and where. Thus it becomes necessary for the physician to understand the blood supply to the brain. There are two main vessels that supply the brain—the internal cartoids and vertebrals.

The vertebrals give off the anterior spinal and posterior inferior cerebellar arteries (both of which supply branches to the medulla oblongata), and unite at the caudal level of the pons to form the basilar. Branches of the basilar include the transverse pontine, anterior inferior cerebellar, superior cerebellar and posterior cerebral arteries. The basilar ends rostrally between the crura cerebri by dividing into the posterior cerebrals. These vessels are joined near their origin by the posterior communicating branches of the internal carotids, and thus form part of the circle of Willis. Branches of the posterior cerebral arteries are distributed to the mesencephalon, the posterior and upper part of the diencephalon (including the geniculate bodies, pulvinar and chorioid plexus of the third ventricle), the lower temporal cortex and to the medial occipital (calcarine) cortex.

The other major vessel — the internal carotid furnishes:

(a) Opthalmic artery to optic nerve, eye and orbit.
(b) The posterior communicating.
(c) Anterior choroid which runs to the descending horn of the lateral ventricle and supplies the uncinate gyrus of the temporal lobe, the choroid plexus of the lateral ventricle and the ventral part of the internal capsule.

Terminally, the internal carotid divides into the anterior and middle cerebrals which have as their branches the striate and lenticulostriate arteries.

There are certain sites of prediliction for strokes which are as follows:

1 The major bifurcation of the middle cerebral.
2. The anterior cerebral at its origin and as it curves around the genu of the corpus collosum.
3. The vertebral arteries near their junction to form the basilar artery.
4. The upper bifurcation of the basilar artery—and—

5. The post cerebral artery as it winds around the cerebral peduncle.

The results of a vascular occlusion vary depending on the availability of collateral circulation. Thus, certain conditions such as the endarteritis from syphilis may produce only transient symptoms.

1. Middle Cerebral Artery — contralateral hemiplegia, cortical sensory deficit (cortical hyperesthesia) and hemianopsia. If on the dominant side an aphasia results. If the deep territory of the middle cerebral (lenticulo striate artery) is involved the upper part of the posterior limit of the internal capsule and adjacent basal ganglia become affected resulting in a complete hemiplegia (face, arm and leg) because the motor fibers are so closely packed in the capsule.

2. Anterior Cerebral Artery — results in a paralysis and cortical hypesthesia of the opposite lower limb, and mild involvement of the opposite arm, mental changes of the dementing type, ataxia of the upper extremity, grasping and sucking reflexes and incontinence of bowel and bladder (frontal lobe incontinence).

3. Post Cerebral Artery—

a. When superficial the hippocampotempero-occipital region is involved and a hemianopsia results. If the dominant hemisphere is involved alexia and some temporary mental changes occur

b. If deep it involves the thalamus and brain stem and produces a contralateral hemiparesis and thalamic syndrome (which is a contralateral cerebellar ataxia and a N3 palsy). If bilateral involvement occurs it results in a cortical blindness but the person is unaware he cannot see.

4. Vertebral Artery — involvement results in a lateral medullary syndrome (syndrome of posterior inferior cerebellar arteries — Wallenbach Syndrome) consisting of facial pain, rotational vertigo, vomiting dysphagia, ipsilateral cerebellar ataxia, contralateral loss of pain and temperature sensation on the extremities and trunk and homolateral involvement of the face.

5. Basilar Artery — which supplies the pons and the territory of the posterior cerebral artery including the midbrain thalamus and temporo-occipital lobes of the cerebral hemispheres. The brain stem involvements cause bilateral pyramidal tract symptoms combined with either unilateral or bilateral cranial nerve palsies (III to XI). The clinical picture is weakness to paralysis of all four extremities, increased reflexes, bilateral Babinski signs, dysphagia, diplopia, numbness of face, weakness of masseter muscles, and deafness. In addition if patient is not comatose or stuporous a rotational vertigo, cerebellar atoxia and a long tract sensory deficit is noted (spinothalamic or medial leminscus).

Until recently the involvement of the internal carotid artery was usually diagnosed as middle cerebral syndrome but with the use of angiography many such cases were shown to be a partial or complete involvement. If complete the anterior cerebral and opthalmic vessels were also involved but depended on the adequacy of the anastomatic vessels of the circle of Willis.

Until recently it was sufficient for a physician to just appreciate the patient had a stroke and the type was of little consequence. If it was mild the patient recovered and if severe the patient died. Now the situation is rapidly changing. Drugs are used which alter the coagulability of the blood, dilate blood vessels, suppress endocardial and hemic infections, reduce blood pressure, elevate it after circulatory collapse. In addition, neurosurgical techniques have been devised and perfected so that surgical control of hemorrhage, the removal of clots and the replacement of diseased segments of arteries by grafting are all feasible today. Therefore accurate diagnosis is imperative and the examination of the spinal fluid is of even greater significance.

The most common type of stroke, (i.e. 50% of the cases), is the thrombosis with atherosclerosis. The atherosclerosis is the primary disease and the thrombosis is added later. Because of the tendency to form at bifurcations, branchings and curves the sites of occurrence of thrombus formation is greatest at these points. The sites of predeliction were discussed

previously. The clinical picture of thrombosis is:

1. Prodromal episodes of recurrent cerebral ischemic attacks with recovery or improvement between them.
2. Gradual evolution with progression of symptoms over a period of hours to days.
3. Relative preservation of consciousness.
4. Clear cerebral spinal fluid
5. Evidence of atherosclerosis elsewhere.
6. Presence of disorders commonly associated with atherosclerosis such as diabetes, hypertension.

The other clinical conditions it has to be differentiated from are subdural hematoma, embolic occlusion, primary subarachnoid hemorrhage, intracerebral hemorrhage and hemorrhage from vascular malformations.

Embolic occlusion symptomology is:

1. Symptoms develop suddenly without prodromal manifestations.
2. Source of emboli as in cardiac conditions.
3. Other evidences of emboli in
   a. Other organs.
   b. Other areas of brain.

Subarachnoid hemorrhage is characterized by:

1. Sudden onset of headache.
2. Antecedent epilepsy or focal cerebral symptoms.
3. Cranial bruit.
4. In young people.
5. Bloody spinal fluid.
6. No hypertension.
7. Pre-retinal hemorrhages and/or retinal angiomas.
8. Calcified areas seen on skull X-rays.

Once the exact diagnosis is made, attention must be focused on the final phase of this problem namely, treatment. The scope of this article will be limited to anticoagulant therapy. Hedenius[3] used heparin in 1941 in 18 cases and found only favorable results in 5 cases, uncertain results in 10 and insignificant results in 3. However Willikan, Scekert and Schick[4] in 1955 used anticoagulants in 26 cases and reported excellent results—transient episodes ceased in 5 cases and the mortality from thrombosis was reduced from 43% to 14%. In 1958 C. Miller Fisher[5] reported on the use of anticoagulants in 58 cases using 38 cases as controls. The unfavorable results were in fully developed strokes of several days duration. However, when used early satisfactory results were obtained.

The use of heparin and dicumerol has dissipated the hopelessness that has long surrounded the occurrence of a stroke. They have been shown to be very useful in the early stages of progressive paralysis due to thrombosis and give excellent results if given at the time of the prodromal transient ischemic attacks.

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CHEMOPALLIDECTOMY

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Chemopallidectomy is a term coined by Dr. Irving Cooper in 1954. The term describes the procedure whose ultimate aim is the destruction of part or all of the globus pallidus by chemical means. For a considerable time, neurosurgeons have been attempting to develop a surgical technique which would eliminate the symptoms of the hyperkinetic disorders, chief among them, Parkinson's Disease. For the most part, these operations have involved interruption of the pyramidal tract, either at the level of the cerebral cortex, the cerebral peduncles, or the spinal cord. Clearly, therefore, they resulted in a sacrifice of motor power for the relief of the hyperkinesis. Russell Meyers[1], in 1942, reported a transventricular approach to the pallidofugal fibers in the treatment of Parkinson's Disease. He concluded that the risk of this operation was too great but his conclusion stimulated further study in the direction of the basal ganglia. Spigel and Wycis[2], in 1954, Fenelon and Thebault[3], in 1950, Narabayashi and Okuma[4] in 1953 and Wyatt and Brion[5] in 1953 all devised procedures aimed at the destruction of certain portions of the basal ganglia. In 1952, Cooper first described a series of forty cases of occlusion of the anterior choroidal artery which showed alleviation of the tremor and rigidity of Parkinson's Disease. As time went on, it became apparent that the significant area destroyed by all these procedures was the medial globus pallidus.

Because of the relative danger associated with ligation of the anterior choroidal artery and because of the fact that the results of ligation of this artery were not invariably salutary, Cooper devised a means of injecting novocaine into the area of the globus pallidus to determine whether or not destruction of this area would result in alleviation of the Parkinsonian tremor and rigidity. If the novocaine alleviated the symptoms, anterior choroidal ligation was undertaken. This test, which anticipated the effectiveness of ligation of the anterior choroidal artery, soon, logically, became the actual procedure for destruction of the globus pallidus by substituting more permanent destructive chemicals for the novocaine and eliminating the anterior choroidal ligation. Over the period of the last four years, Cooper and his associates have devised newer techniques, constantly improving the accuracy of localization and the destructiveness (and permanency) of the chemical instilled into the globus pallidus.

Though it would be of historical interest to detail all the various techniques which have been involved, the current procedure in use will be the only one described. We do not follow the Cooper technique precisely as outlined by him and have evolved certain modifications of our own. The fundamental technique, however, is entirely that described by Cooper. The patient's head is shaved entirely following which radio-opaque wire is taped to the mid-sagittal plane of his scalp. Another radio-opaque wire is taped 13½ centimeters behind the nasion in the coronal plane. These wires serve as landmarks prior to the surgical procedure. The patient is placed in a sitting position with the head bent forward, following which spinal needles are inserted into the subarachnoid space usually at the 3rd or 4th lumbar intervertebral space. 40 ccs. of spinal fluid are removed and replaced with 40 ccs. of air in 10 cc increments. The head is kept bent forward, following which the needles are removed.

The patient is then placed in the supine position on the operating table and an antero-posterior and transverse lateral beam x-ray of the skull is made. These x-rays made under normal circumstances, reveal the anterior portion of both lateral ventricles, the foramen of Munro

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and the anterior portion of the third ventricle. With the landmark wires in position, one is able to judge the exact location that is desired for successful destruction of the medial globus pallidus. The wires are then removed from the scalp. Immediately following this, a scratch is made in the midline of the scalp to note permanent identification of the sagittal midline. If the wire which passed through the choroidal plane 13½ centimeters behind the nasion appears, on the pneumoencephalogram, to be passing through the foramen of Munro, a scratch is made at this point. If modifications are necessary forward or backward, the scratch is made at whatever modified choroidal plane seems indicated. This scratch is then crossed by another scratch 5½ centimeters from the midline. This cross now is the point at which a burr hole will be placed. The head is then carefully prepared and draped with special draping technique which allows the patient's entire body to be visualized and muscular function to be tested during the course of the surgical procedure. Instruments cannot be used to fix the drapes in place on the scalp since the procedure is constantly under x-ray control and metal instruments would interfere with the visualization. Consequently, all the drapes are sewn directly to the scalp under local anesthesia (without adrenalin). The area previously designated by the cross scratch is now infiltrated with novocaine (containing adrenalin to diminish vascularity). An inch and a half incision is then made through scalp, galea and periosteum, and a self-retaining retractor is inserted. A routine burr hole is made in the area and the dura incised in a radial manner. The arachnoid is then pierced. At this point there are numerous "chemopallidectomy guides" which can be affixed to the skull in order to give more accurate and unvarying direction to the cannula which is to be inserted. It has been our experience, however, that a "free hand" insertion of the cannula is more expeditious and accurate. One of us places a mark one finger's depth from the mid-line at the nasion and aims the cannula in that direction. The cannula is composed of polyethylene and, like a Foley catheter, has a small inflatable rubber bag at its very end. This bag has a capacity of half cubic centimeter. In effect, therefore, the cannula is actually two cannulae with two separate openings at the hub end of the needle. The trochars for the actual cannula are of two kinds. The first is a solid metal trochar which allows very little bending of the cannula. It is radio-opaque and is employed in the initial search for and final placement of the end of the cannula in the medial globus pallidus. The second trochar is just as malleable as the polyethylene tube and has, at 1 centimeter intervals along entire length, radio-opaque pieces of metal. Thus, after the cannula is in place, constant x-ray visualization of this location is available to the surgeon.

At this point, the operator is now ready to insert the needle in his primary search for the medial globus pallidus. The eventual aim of the needle point is at the tip of the cannula. The eventual aim of the cannula point is demonstrated in figures 1 and 2. In the antero-posterior x-ray (Figure 1) it is desired that the point of the cannula end where the following two lines coincide—a line drawn horizontally through the middle of the third ventricle and a line drawn perpendicularly through the lateral third of the lateral ventricle. In the lateral pneumoencephalogram (Figure 2) it is desired that the cannula pass through either the foramen of Munro, slightly posterior to it, or if the foramen of Munro is not visualized, through the posterior clinoid.

The cannula is then inserted to a distance of a centimeter and a half in the direction that the surgeon considers the proper one. At this point, one of us places a supporting sling of silk suture around the cannula so that its weight does not cause it to drop out of the cerebral cortex. An x-ray is then made in the antero-posterior and lateral positions. The direction of the needle is then projected by scratching its direction directly on the x-ray film beyond the actual penetration of a centimeter and a half. If it ends up in the proper planes described above, the needle is then inserted to a distance of anywhere from 5 to 6½ centimeters, varying with the size of the patient's head. The firm trochar is then removed and a small

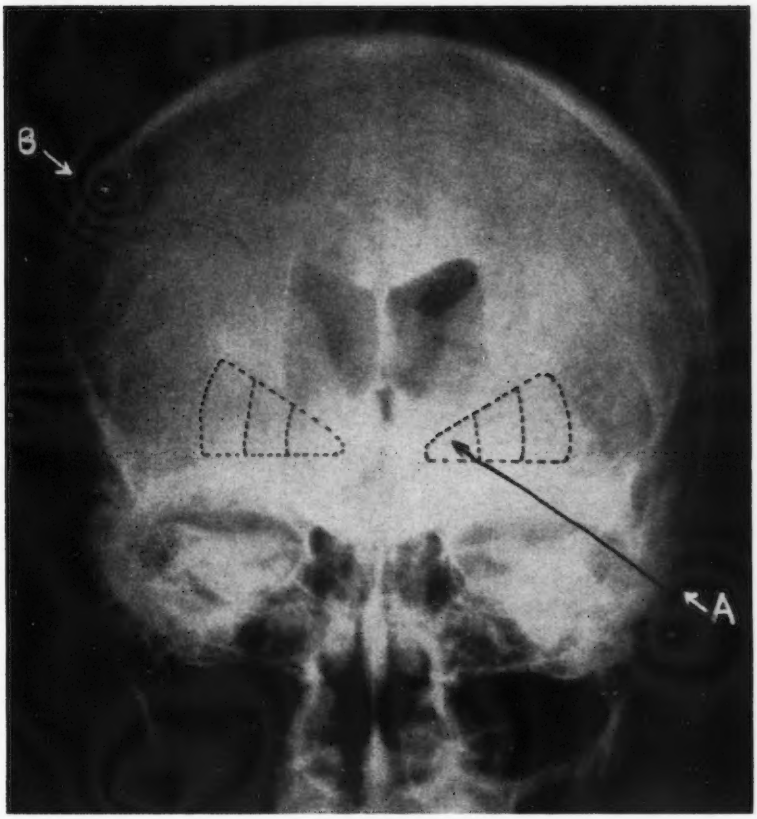

FIGURE 1

degree of negative pressure applied to the hub of the cannula to determine whether or not blood or cerebral spinal fluid is returning. If the cannula is dry, the distal bag is then filled with ½ cc of hypaque and a repeat x-ray made to determine whether or not the hypaque bag (which is the exact end of the cannula) is in the proper plane. If such is the case, the cannula is then fixed in place with silk sutures and the wound closed with black silk in layers. Although no destructive chemical has yet been instilled into the patient's globus pallidus, the pressure of the ½ cc bag which has been expanded in the depths of the medial globus pallidus frequently causes enough destruction, so that immediate alleviation of the tremor and rigidity of Parkinsonism (on the opposite side) can be observed. It is to be noted that the pliable trochar is the one that is inserted following the fixation of the cannula in place.

The patient is observed constantly over a period of the next one or two days. If no untoward symptoms are seen after two days, the hypaque is emptied from the bag at the end of the cannula. A cavity ½ cc in size has thus been manufactured in the depths of the medial globus pallidus. Into this cavity ½ cc of etopalin is injected slowly, and the trochar returned to the cannula. The cannula is allowed to remain in place for several more days. If the symptoms of Parkinsonism begin to return, another ½ cc injection may be made. If the symptoms do not return, it is left to the surgeon's judg-

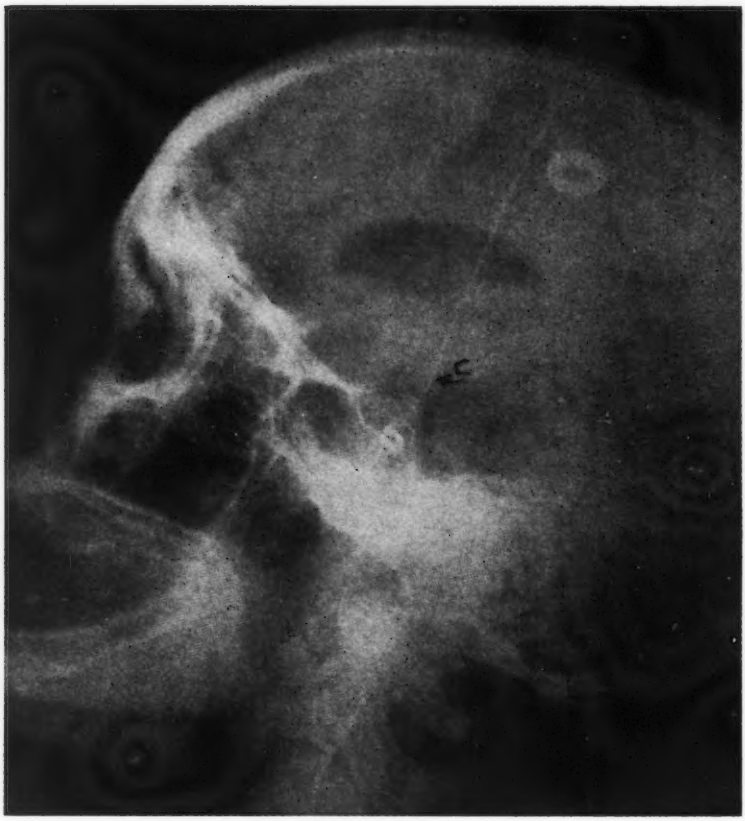

FIGURE 2

ment as to whether or not more destructive chemical should be instilled. As many as three injections can be made. Before each injection, it is mandatory that an x-ray film of the patient's skull be made to be sure that the position of the cannula has not changed. When the surgeon is sure that his result is relatively permanent, the cannula is removed.

The mortality rate of Chemopallidectomy varies and is reported to be anywhere from 3 to 12 per cent. We have had two deaths, one resulting from post-operative hemorrhage occurring four days post-operatively into the cerebral hemisphere and other secondary to basilar meningitis which occurred several weeks following the surgical procedure. In the latter death, the patient removed his bandage during the immediate post-operative period of confusion, opened the surgical wound with his fingers and placed his fingers into the actual cerebral structure. Hemiplegia and residual hemiparesis must always be considered as a possible post operative complication. Facial parlysis is very frequently noted following the surgical procedure but it invariably disappears. Ataxia, extra-ocular palsies, periods of mental confusion and negativistic behavior are frequently seen. Almost invariably these complications clear up spontaneously.

The success of this procedure for the alleviation of the symptoms of Parkinsonism (and other hyperkinetic diseases)

seem to be unequivocal. On the other hand, it is our carefully considered opinion that a number of the glowing reports currently appearing in the literature may be colored by the surgeon's enthusiasm. We feel that Chemopallidectomy is a relatively safe and reasonably successful surgical procedure in the treatment of hyperkinesis.

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MANAGEMENT OF MENINGITIS AT COOK COUNTY CONTAGIOUS DISEASE HOSPITAL

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Before discussing our method of treatment a few words should be said in regard to meningitidies. It is well known that all forms of meningitis are not communicable. Usually the meningococcic are the only communicable ones. However, tuberculous meningitis is sometimes included on the theory there may be an open pulmonary lesion. Of course if such is the case it is a contagious disease.

In view of the foregoing facts one may wonder why all varieties of meningitis are sent to an isolation hospital. In reality there may be a good reason for doing so. In the first place the meningococcus is generally the causative organism for most cases of meningitis. It is therefore immediately thought of and is under suspicion. It should also be kept in mind that an isolation hospital is not merely for the admission of patients with a definite diagnosis of a contagious disease but also for those suspected of having a communicable infection.

Sometimes due to an erroneous diagnosis the patient is sent to an isolation hospital. Possibly there are a few blemishes on the skin which have been mistaken for petechiae. If there are actually petechiae in the skin or perhaps the conjunctiva and the patient has meningitis it is almost certain that meningococci are invaders. The rose spots of typhoid fever, petechia of typhus, endocarditis and septicaemia have been known to be misleading, however. Measles which "anyone can diagnose" has also been mistaken for meningococaemia.

Examining Room—Careful observation is made for the possible presence of any petechiae. If petechiae are found a smear is made and stained to determine if it discloses gram negative diplococci. If the smear is positive no lumbar puncture is made. Otherwise a spinal tap is required for every case or suspected case of meningitis. A smear and cell count of the spinal fluid are made by the interne or resident. A culture and complete chemistry of the spinal fluid report is obtained from the main laboratory. A blood culture is also required from every case or suspected case of meningitis. If the patient has definite signs of meningitis and cerobrospinal fluid yields a negative smear, a sample of the fluid is sent to the virology laboratory for tissue culture. This action is taken to determine if the patient has a viral meningitis. Many cases formerly diagnosed as "aseptic meningitis" are now thought to have had the virus Echo 9 as the etiologic agent. Other viral agents have also been found responsible in some cases of meningitis.

Sensitivity tests with several antibiotics which seem appropriate for the patient should be resorted to as soon as labocatory diagnosis is established. There may be guides[1] which are often helpful in the clinical diagnosis before laboratory reports are attainable. The significance of petechiae has been referred to. If the meningitis patient has a history of an old skull fracture, a pneumococcic infection should be suspected. A chronic otitis media may also give rise to a similar thought. If there is or recently has been a severe infection of the upper lip area streptococci should receive consideration as the possible invaders of the meninges.

Age may be a contributing aid in the clinical diagnosis of meningitis. It has been estimated that 90% of patients who develop haemophylus influenza meningitis are under 5 years of age. Influenzal meningitis occurs with great rarity in adults and is uncommon over 10 years of age. In infants under one year E coli may deserve some thought as an attacker of the mininges. With young children who have tuberculous meningitis it is not unusual to find there is an inequality

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of pupils. This observation is very rarely witnessed in the early stage of other kinds of meningitis. Chest findings may also add value to the belief that there is a tuberculous infection, and a Mantoux test may affor support to such a conclusion.

Treatment—For safety every meningitis patient, with the exception of infants, should have a restraint on at least one extremity, otherwise an irrational patient may get out of bed and plunge through a window. Sedatives however are not required for every patient. Morphine should never be given. It depresses the respirations. Under no circumstances is there recourse to intrathecal therapy[2]. This mode of treatment was abandoned by one of us more than 20 years ago when a shift was made from the customary intraspinal antiserum for meningococcic meningitis to the intravenous route. At the present time however some physicians continue to advocate the intraspinal route for therapy. They apparently believe that for pneumococcic meningitis in particular penicillin must be administered in such a manner. We are in total disagreement with such a view and have ample evidence to uphold our opinion. Some writers also maintain that the sulfonamides are preferable to the antibiotics for the treatment of meningitis. Others feel that a sulfa drug should be prescriped as well as an antibiotic.[3] We are not convinced that either one of the foregoing assertions is justified. Our own experience moreover affords a strong foundation for our thoughts. We have almost completely discarded the administration of sulfonamides for meningitis patients because we think they are unnecessary when appropriate antibiotics are used.[3, 4, 5] Furtheremore the sulfonamides sometimes cause unpleasant reactions—rashes, hematuria and even agranulocytosis.

There is another procedure which is often performed without sufficient thought. For several years past, tapping to determine if there was a subdural effusion was at the height of its popularity. If a meningitis patient did not have a normal temperature after 3 to 4 days treatment, someone would "thoughtfully" suggest that there might be a subdural effusion and advise an attempted aspiration. We know that subdural effusions can and do occur. Nevertheless every child that has an open fontanelle with evidence of slight tenseness does not need a puncture.[6] As time passes on the worry in regard to the assumed frequency of subdural effusions seems to have diminished considerably. Prior to discussing our recommendations for medication there is at least one more bit of advice to offer. Too much thought should not be given to the dangers of increased intracranial pressure. Years ago this was almost a fetishism, especially among neurologists. Frequent lumbar punctures should not be done for the "purpose of relieving intracranial pressure". Such action seems to stimulate an increase in the amount of cerebrospinal fluid. There are also a number of other objections to such treatment; for example, pseudomonas meningitis is frequently due to direct introduction of this organism into the spinal canal.[7]

Selection of a suitable drug—Some physicians have advised that no antibiotic should be administered until a definite laboratory diagnosis has been established. Again we disagree. Treatment should begin at the earliest possible moment following a presumptive diagnosis. Penicillin is not the preeminent antibiotic to choose. One might assume from some published reports that penicillin is the only antibiotic effective when treating pneumococcic meningitis. We believe that the tetracyclines are equally efficient as penicillin. Moreover the tetracyclines give excellent results in the treatment of influenzal meningitis but penicillin does not. [3, 4, 5] Meningococci are also subdued by the tetracyclines with the utmost satisfaction with moderate dosage whereas penicillin would require millions of units. Our motto might be "when in doubt as to the clinical diagnosis of meningitis prescribe a tetracycline while awaiting laboratory disclosures." Furthermore, even though sensitivity tests show that some other antibiotic should be more efficient do not necessarily change the drug if the patient is making good progress toward recovery.

For tuberculous meningitis patients

TYPE	AGE RANGE	TETRACYCLINE ALONE					MULTIPLE ANTIBIOTICS				
		No. of Cases	Recovered	Complications	Deaths	Remarks	No. of Cases	Recovered	Complications	Deaths	Remarks
Meningococcic	1½-30yr	2	2	0	0	-	4	3	Hearing impairment in patient admitted in coma, and also found to have amebiasis.	1 after 9 days	1 death-also had pulmonary atelectasis and + blood culture for hemolytic staph albus.
H. Influenza	15mo-5yr	3	3	0	0	-	3	2	Moniliasis of mouth in one patient.	1 after 8 days	Patient that died admitted from another hospital after 2 days of no therapy.
Pneumococcic	3¼-45yr	2	2	0	0	-	1	1	Moniliasis	0	Did not receive pen. because of allergy.
Streptococcic	7yr	-	-	-	-	-	1	1	-	0	Thought to be TBC on admission and placed on streptomycin and nydralid. Then placed on tetracycline.
Staph. Aureus	2yr	-	-	-	-	-	1	1	-	0	Chloromycetin alone.
Purulent C.S.F. No growth	4yr-17yr	1	1	0	0	-	2	1	-	1 after 6 days	-
Clear CSF 150 cells No growth	15yr	1	1	-	-	-					
		Total No. of Cases 9			Total of Deaths 0		Total No. of Cases 12			Total of Deaths 3	%Fatality 25%

Total No. of Cases: 21
Total No. of Fatalities: 3 14%

Meningitis cases (excluding two TBC) admitted to Cook County Contagious Disease Hospital, Jan. 1, 1958 to June 30, 1958.

the management is much the same as that which has been described. The choice of an antibiotic lies between streptomycin and dihydrostreptomycin. It now seems that the former is preferable. Originally the latter was claimed to be less toxic. Isoniozid is a valuable drug also and should be administered. Eventually it may entirely displace streptomycin for the treatment of tuberculous meningitis patients and has the advantage of being orally acceptable.

Route for Administration of Remedies—We feel that it is advisable to give the initial dose of the chosen drug intravenously if it is suitable for that route. It may be given in either 5% or 10% glucose in distilled water by the drip method, and the same procedure can be repeated if it seems advisable. Otherwise the intramuscular route is adopted until the patient is in a condition to accept medication orally.

Special Measures of Therapy—In cases of the Waterhouse-Friderichsen syndrome the immediate necessity is the treatment of shock. This condition is very rarely due to any other organism than the meningococcus. But there may be no evidence of meningitis. The skin is likely to be studded with petechiae and there are often large hemorrhagic areas. Whole blood transfusions and an oxygen tent are helpful. The steroids and more recently norepinephrine have been recommended. Nevertheless the true value of these two remedies is still somewhat uncertain.[8] Prior to 1946 there appears to have been no reliable report of a Waterhouse-Friderichsen patient who survived. We have seen fatal cases where the patients had symptoms pointing toward the Waterhouse-Friderichsen, but at autopsy no hemorrhage was found in the adrenal glands. Regardless of any doubt that may exist in respect to the therapeutic worth of the steroids, a Waterhouse-Friderichsen patient should not be deprived of any measure which offers the possibility of helpfulness.

The accompanying table shows briefly the number of meningitis patients treated in Cook County Contagious Disease Hospital during the first six months of 1958. This table does not include two cases of tuberculosis meningitis; both of which were being treated successfully with intramuscular Streptomycin and oral Isonyazid. The authors do not consider the figures as conclusive proof that tetracyclines should always be given alone. This chart however, is quite representative of our experience in recent years; and we feel strongly that where the causative organism will respond to one antibiotic, two or more are unnecessary and of no increased value to the patient. This is further borne out in the chart by noting that three of the eleven patients, given multiple antibiotics, expired in spite of this "heroic" therapy.

Medication is usually discontinued after temperature has remained at a normal level for at least forty-eight hours. The patient is required to be out of bed for a minimum of one day prior to his release from the hospital. He is also requested to report to our examining room, if after his return home, any illness develops which seems to be related to his hospital stay.

Comment—Our chief points of emphasis in this discussion of meningitis has been as follows: (1) make a prompt clinical diagnosis (2) do not wait for laboratory reports before starting treatment. This latter statement is contrary to advice sometimes given with the explanation that drugs may prevent or make difficult laboratory procedures for determining the presence of an organism. As a rule however, the patient has had no medication at the time specimens are obtained. (3) select an antibiotic which is known to be effective against several different kinds of bacteria. Even if the clinical diagnosis is proved to be wrong, the treatment may be correct. One should keep in mind that the primary purpose of treatment is to bring about recovery. (4) do not give aspirin on the first day of treatment to lower the temperature. Remember, the fever is due to the infection. If the antibiotic administered is suitable, the temperature will decline; otherwise it is not likely. (5) do not, under any circumstances, resort to intrathecal therapy nor make repeated lumbar punctures to reduce intracranial pressure. (6) do not make a hasty decision that there is a subdural effusion which requires aspiration.

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DIAGNOSIS — DISCUSSION OF A MEDICAL CONCEPT

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In the course of his medical education, the student is constantly reminded of the scientific basis of his medical studies. Deductive and inductive reasoning is continuously applied to the task of developing a diagnostic estimate about a patient's illness. A logical process of evaluating positive and negative factors is developed into a differential diagnosis, and a final or definitive diagnosis. This emphasis has tended to lull the physician into a sense of satisfied self assurance, best expressed in the cliche: "I have done a complete diagnostic workup," or "I have ruled out everything else." There is a need for questioning the depth of our self assurance about the validity or finality of diagnostic conclusions. Diagnosis and differential diagnosis are constantly suggested as one of the goals of the physician in the initiation of the interview and examination of the patient. Surely without adequate diagnosis, the therapeutic goals for a patient will of necessity be limited to a great degree. And it is customary to make the diagnosis in accordance with the established official nomenclature of disease process.

Some of the difficulties with the problem of effective diagnosis are, of course, related to the adequacy of the examination, and the knowledge and experience of the examiner. It goes without saying, that an examiner who has never heard of, read about, or seen a condition, will not be able to diagnose such an illness from which his patient may suffer. More frequently a diagnosis is not established because of failure to examine properly, or inability to evaluate adequately the findings elicited in the examination. Probably the most significant factor in failing to diagnose adequately, or to develop an effective differential diagnosis is incompleteness of the data obtained in the history. The diagnostic interview should rarely, if ever, be considered completed, must never remain static, and can always reveal further data which must be integrated with information obtained from the physical examination, the laboratory, and the personal interviews with the patient and family.

Special problems of diagnosis exist in some areas where classification of diseases, nosology, is obscure. Many of the syndromes which are seen clinically and interpreted have a low correlation for diagnostic agreement about the same patient by several different examiners. This is seen often in psychiatric diagnoses, and in the medical and surgical specialties whenever the syndrome is not very definitely or "typically" established by clear cut mutually exclusive symptoms and signs. Szasz[1] has emphasized the problems of diagnosis when the nosology does not fit a variety of situations in which the same clinical material is being viewed from different operational frames of reference. He believes that the same system of classification is not operationally practical for clinic, mental hospital, private psychiatric practice, military service, or court of law and jail. One can certainly say that the relationship of classification of "disease" and diagnoses, as made clinically, are not without the problem of some incompatability between what is an operationally sound conclusion and the clinical diagnosis strictly according to nosology. The laboratory, the clinic, and the individual physician might all give a different diagnostic expression about the same patient, and each be internally consistent about it.

Study of the Patient as a Total Field:

There are many facets of this "scientific" evaluation of the patient which could be discussed with profit to both the physician and the patient. Firstly, it is suggested that the process of diagnostic appraisal may best be understood in terms of the study of a total field which includes (1) the patient: as comprehensive a grasp of his total life experiential background as one can obtain; (2) the current situation: data with regard to onset and course of the present illness which brings him for examination to; (3) the physician: his personality, his

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knowledge, skills, and the particular "sets" or preferences with which he initiates his appraisal of the total field. Part of that field includes the basic motivations of the physician in the doctor-patient relationship. The appraisal therefore includes a certain amount of self scrutiny.

As Szasz[2] has indicated physicians have traditionally been interested in "things" such as anatomical structures, lesions, bacteria, and the like. This traditional interest has colored concepts of etiology, pathology, diagnosis and treatment of the patient. He describes three basic models of physician-patient relationship. (See Table I.)

Model	*Physician's role*	*Patient's role*	*Clinical application*	*Protoype of role*
1. Activity possibility	Does something to patient	Unable to respond or inert	Anesthesia, acute trauma, coma, delirium	Parent-infant
2. Guidance cooperation	Tells patient what to do	Cooperation, obeys	Acute infectious processes,	Parent-child, or adolescent
3. Mutual participation	Helps patient to help himself	Participant in partnership, uses expert help	Most chronic illnesses, psychoanalysis, psychotherapy	Adult-adult

TABLE I.

In the diagnosis and differential diagnosis of the patient the physician tends to function within the framework of one of these model relationships as a prevailing pattern. The relationship is seldom exclusively either one or the other type. Elements of all three model relationships usually exist, but one model will be evident as the prevailing relationship. There is another role in which the relationship is that of an instructor. The physician is often in controlling or interacting relationship with two persons, a patient and a spouse or parent. The patient may consider himself somewhat accountable for his own acts to a close person, who in turn considers himself or herself a colleague, or monitor for the physician-instructor. Prototypes of this three way relationship are seen in grandparent-parent-child-grandchildren relationships. How the investigation leading to a diagnosis is influenced by various model relationships is in itself an item for considerable investigation.

An example of the influence of the various relationships might be helpful in clarifying the effects on diagnosis. A patient presents himself to the physician with complaints of feeling ill with some malaise, muscular aches, headache and slight coryza. The temperature is 99.4 by mouth, the physical examination non-revealing except for evidences of nasal congestion and a slightly congested throat. The physician with a strong set toward an activity-passivity relationship, and a strong need for perfection in his diagnostic evaluation may order the patient to have a chest plate taken, a blood count made, and may even insist on his going to bed and remaining there until he can be seen again. The chest plate may reveal evidences of an old tuberculosis with some suggestive findings in the hilar area and in the area of the healed lesion. A diagnosis of tuberculosis is entertained and further diagnostic studies made. No further corroborating evidence of an acid fast condition is found. The temperature subsides and the patient recovers; the final diagnosis, "old healed tuberculosis." In model two both participants contribute. The patient presented his problem and having been examined is told that the problem is one of a respiratory infection which requires bed rest and medication. The patient responds by indicating that previous chest examinations showed some pathology. "Could this be a flare up"? The patient is told that the diagnosis is rather clear. The old chest pathology is probably not related to the current complaint, but since the patient is concerned, an X-ray of the chest is being ordered. The diagnosis made is upper respiratory

infection, old healed tuberculosis. The relationship now to be depicted is the adult to adult model. Noting the expression of concern, "Could this be a flare up?", the physician may explore the question more fully, and may find that the patient has many obsessive concerns about illness, and particularly is concerned and preoccupied with fears of contamination, and the spreading of tuberculosis. He feels that the findings of respiratory infection with absence of real evidence of tuberculosis warrants his telling the patient that he has a cold, that there is no evidence of tubercular flareup and that since an X-ray was taken only two months ago that he merely will check on how the cold is in about a week. He believes that the patient would not have made the medical visit had he not been suffering from the neuroses. Diagnosis made on the model three relationship might then read: psychoneurosis, obsessive compulsive type; upper respiratory infection; history of tuberculosis requires further study and evaluation.

Motivation and Diagnosis:

The aspect of evaluating motivations of the patient, which bring him to the doctor with his illness, is especially worthy of note in arriving at a diagnostic appraisal. The patient's motivation for seeking help may be seen by the physician too exclusively in terms of correction of the defect in which the physician has a specialized interest. This seems to be a common factor in the final diagnostic choice, and one which leads to peculiar incongruities between what the patient thought he was seeking help for, and the treatment he was given. To quote Edmund Bergler: "A girl of eighteen may develop a nervous stomach and after treatment by a gastroenterologist be helped. Two years later she may suffer from migraine headaches, and a neurologist is consulted. In the meantime she has married and divorced two husbands. After her return from Reno, she has severe abdominal pain. Appendicitis is suspected. A laparotomy is performed but the appendix proves to be normal. A few months later the headache sets in again. She consults a neurologist. Later the patient complains about all sorts of ills, and consults in rapid succession a gynecologist, an internist, and a sinus specialist. All her life she remains a patient of universal medical science, a non-improving neurotic."[3] This statement highlights a problem of diagnosis, functional disorder, and specialization.

The problem of personal gain is one which requires much further investigation and elaboration than is normally given. Obviously this aspect of the reason for a patient's diagnosis will vary considerably with the economic status, security and strivings of the physician. To all these factors in his personality must be added the economic status of his social group, his own aspirations about acquiring wealth, as well as the significance of wealth in the particular culture in which the physician works. Our situation is further complicated because the physician is in a unique kind of human endeavor in which considerable emphasis is placed on his subordinating personal gain to the best interests of the patient. All things considered, it is really remarkable that the physician can do as well as he does in setting aside personal gain as a motive for diagnosis.

Unconscious factors may operate in helping direct diagnostic considerations in a certain direction. The need for prestige, recognition, and acclaim may be readily inferred when diagnostic consideration leads one to "prove" the presence of some unusual and rare disease, demonstrating that we understand and can diagnose this disease, whereas a previous examiner failed to be that learned and perceptive. Colleagues and others are to be impressed with the number of cases in a certain category known to be relatively unyielding to current therapeutic procedures, but which were treated successfully. Neurotic fears may prevent the physician from making a dreaded diagnosis, as if, by so doing, he is to blame for the illness. Fears of success in competition for a correct diagnosis against an older, respected colleague may lead one to misinterpret facts that have been gathered, or fail properly to develop other facts which may lead to a correct diagnosis. A need for extreme orderliness and logical progression may cause the

physician to be irritated with what he feels is a mass of irrelevant and circumstantial, repetitive material, without appreciating that from these may be inferred validly the essence of the patient's problem. Or the non-communicative patient may exasperate the physician who wishes to have material given to him freely and easily. He becomes annoyed that the patient seems to withhold and delay failing also to recognize in the withholding process, a sign of the patient's illness.

The Complete Diagnostic Workup:

The "complete diagnostic workup" has become a well established necessity for adequate diagnosis. But it is difficult to determine when a "complete" workup is completed. An adequate history, a physical examination and appropriate laboratory procedures are generally expressed as the essentials of a complete workup. Unfortunately no history is ever really complete. What is accepted as an adequate examination and laboratory evaluation may vary considerably. It is much easier to decide that the workup is not yet complete, than to decide that enough data is on hand to justify making a valid diagnostic appraisal. If, for instance, a patient with headaches, mental confusion, jaundice, and a history of breast surgery some 10 years earlier were not given a liver profile examination by the laboratory, one would consider the workup incomplete. But would the headaches and mental confusion justify skull plates, a spinal puncture, pneumo or ventriculograms, electroencephalographic studies, angiography, a psychiatric consultation, and psychological test battery? Yet if these evaluations are not also made, is it a complete diagnostic workup? All too often a diagnostic workup is considered "completed" when the special or limited interests of the examiner have been satisfied. Such a bias in workup will reflect ultimately on the diagnosis and differential diagnosis of any particular examiner. Specialization may tend to obscure the problem of diagnosis as often as it clarifies.

Unfortunately a workup has often been considered completed with a disproportionate dependence on the laboratory for supplying the "best" information. Any person knowing of or thinking up another test is often then considered as doing the more complete workup. More adequate physical examination, or more extended interviewing may be overlooked as offering help towards such a goal. An example will help clarify this point. A patient with a pain radiating down the inner aspect of the left upper extremity was immediately seen by physicians as needing a complete workup, including an EKG. The same physician did no reflex studies or sensory testing. No cognizance was taken also of a difference in the temperatures of the two hands. The blood pressure study was limited, conventionally, to the one extremity. No examination was made for a cervical rib or any of the signs associated with a scalenus anticus syndrome. Interviewing of the patient was not continued after the EKG was found to be negative, but a diagnosis of angina pectoris was made. Continuous expansion of the physical examination and of verbal information which may be elicited from a patient in repeated visits is infrequently appreciated as a source of the valuable information which can so be obtained. All too often one sees the physician limiting his consideration of further study which may be necessary to just another test. One cannot emphasize too strongly the high probability of eliciting new material vitally needed for diagnostic purposes from continued interviewing of the patient over a series of contacts.

Diagnosis and Presenting Complaint:

The relationship between the presenting complaint and the final diagnosis brings into sharper focus the problem of incongruity between what the patient presents as complaints and the objective for which he is treated. The patient can be viewed as presenting the physician with a problem for solution when he gives his presenting complaints. He is saying, "I present these symptoms for you to work with since you are the expert in understanding them. Now you develop them and tell me what is wrong, what I can expect from what is wrong, and then heal me." One would certainly be surprised and probably irritated with a gas

station attendant to whom one brought a car for an oil change only to find a relatively superficial concern with the oil in the car and maximum interest in the contents of the gasoline tank. If the attendant were to say: "I checked your gas tank, found it 2 gallons short and filled it," and when asked about the oil, responded with, "What difference does the oil make?", we would certainly be irritated. The presenting complaints must be tied up with an associated and relevant diagnostic conclusion in order that we be perceived as logical and realistic in our activities as a physician. A completely unacceptable and inadequate response to a patient's complaints is frequently seen in medical practice. It is not uncommon to have a patient complain of headache and spots before the eyes and end up with a diagnosis of fibroid of the uterus. A presenting complaint of edema of the face and hands may end with a diagnosis of "dumping syndrome." Or vague gastric complaints may be associated with a diagnosis of hemorrhoids. There should be some rational relatedness between what the patient presents as the reason for his visit, and the diagnosis and treatment he receives. Sometimes this incongruous relationship between presenting complaint and diagnosis develops as the physician finds some pathology regardless whether the pathology so observed explains the physiological symptom disturbances of which the patient complains. Only when the pathology so discovered has relevance for the complaint can a diagnosis be justified which is logical for the complaint and the motivation of the visit to the doctor. Pathologic diagnosis based upon coincidental findings should receive secondary notice, but treatment must always be appropriate to the total situation.

Diagnosis and the Ubiquitous Nature of Pathology:

Making a diagnosis which is related to the presenting complaint is sometimes sidetracked by the tendency to relate the diagnosis to conditions which are so general and frequent that they constantly create confusion in diagnostic thinking. Psychological phenomena of clinical significance, and psychopathology can be found in the history of every patient examined by adequate interviewing techniques. The tendency to make a diagnosis of a psycho-social disturbance, and to overlook significant pathologic changes in structure or biochemistry must be constantly guarded against by seeking for life experience data of a traumatic nature, and of psychological disequilibrium adequate in intensity, volume, and relatedness to support such a diagnosis. One must constantly be aware of the possibility of structural disease as a concomitant independent process, or as being responsible for triggering of psychological or behavioral deviations as secondary rather than as primary symptoms.

Almost as ubiquitous as psychological phenomena are structural changes which warrant a clinical diagnosis in the age group over 50. In the ever increasing group of geriatric patients, arthritis, arteriosclerosis, cardiac changes, hypertension, kidney and pelvic changes are almost certain to be found. One must be careful to assess the psychological pathology and relate the complaints to the physiological picture in the degree to which they seem reasonably to fit. Just because organic pathology is found does not give one justification for a diagnostic conclusion which is not warranted by the facts. A most common pattern of complaints in this age group constitutes a depressive syndrome of varying degrees of intensity and duration. All too often a diagnosis in keeping with structural change is made and the much more malignant psychological picture is not recognized, or is misjudged as being appropriate or reasonable in the light of the structural pathology.

The History of the Patient:

In addition to stressing the many distortions in the history which may interpose barriers to valid diagnostic conclusions, we need again to address ourselves to the task of developing a history which focuses on and traces the progress of a symptom through time. A history which develops the important circumstances of the patient's life before, at the time of, and during the development and course of the disturbance is much more likely

to give one the details necessary for developing effective diagnostic conclusions.

Avoiding the introduction of a unique barrier will also be effected if the reported history of a previous illness were to include some supporting evidence. A statement by the patient that he had ulcerative colitis, an attack of diarrhea or coronary disease, when accepted at face value, may lead to unwarranted conclusions. All too frequently, an earlier error in diagnosis or a patient's preference to believe that he had experienced a certain affliction may be followed by a compounding of the difficulty if the incorrect diagnosis is accepted automatically as real in subsequent histories. The recall of the patient about a diagnosis which had been shared with him years ago may become obscured by much overlay in time.

In previous papers,[4,5] we stressed the danger of symptom giving during the course of the history taking procedure. The many distortions in diagnostic thinking that can be created by suggestive symptom giving is readily recognized by the physician. The importance of history taking by an indirect method which eliminates the suggestion of symptoms to the patient is worth re-emphasizing. In my opinion, indirect history taking improves diagnostic accuracy.

Diagnosis Obscured By the Patient:

Often the motivation for seeking medical care is obscured by the patient. He may have many conscious and unconscious reasons to obscure the diagnosis. The physician must constantly be on the alert to appraise the reliability of the patient and of the material being offered. When important facts about the family or personal life are needed, such facts may remain unexpressed, unconsciously blocked, even purposely withheld or voluntarily distorted. Every experienced clinician knows of instances in which essential information was deliberately withheld when it dealt with diseases which might stigmatize the patient or the family, as with syphilis, or create difficulties with regard to marriage or employment, as with tuberculosis or heart disease; or might in the patient's mind lead to a diagnosis for which a painful procedure, such as surgery would be the treatment of choice.

Many important facets of the history may be denied, obscured, glossed over, or withheld, especially when the personal data may deal with facts which embarrass or reflect on the individual. Material with regard to sexuality is especially apt to be so distorted or withheld.[6] One must be alert to such problems particularly in older people because feelings of shame so frequently lead them to deny difficulties in the sexual sphere. A 68 year old woman with a complaint of difficulty in memory and blocking of words was considered to have a possible organic disease of the brain. When first seen she indicated there had never been any sexual problem in her life. Later she was found to have married at age 32 after avoiding men because of an extremely prudish attitude. The death of her first child born within a year of marriage was followed by an agreement with her husband that they would have no more children. For the next 35 years she had no sexual relations with her husband but masturbated frequently, with much guilt and conflict.

Avoiding dealing with certain symptoms characterizes some patients who believe that the proof of the doctor's competence is his ability to discover what is wrong without having been given any hints. Somewhat related is the need not to verbalize certain thoughts or ideas because the words in some magical way predispose one to suffer from the disease being mentioned. This may especially be seen in patients with a cancer-phobia. They will see the physician for a wide variety of physical complaints, consciously wishing to be reassured on that one score. Instead they may stimulate within the physician a determined effort to make some kind of diagnosis. The net result is a game of peek-a-boo with examinations, statements, innuendoes, and allusions. The "something," not verbalized as a fear by the patient nor dismissed by the doctor may be left hanging high. This the patient may take away as confirming his suspicions. In general, it might be said that the anxieties of the patient are crucial factors in determining

the nature of the doctor-patient relationship. The kind of information obtained by which diagnostic conclusions are effected will often reflect the defense against, and attempts to receive assurances for anxieties and fears being experienced by the patient.

Diagnosis and the Family:

How often diagnostic conclusions are influenced and directed by the needs of the patient's family is difficult to evaluate. Sometimes the physician consciously formulates a diagnosis which is at variance with his evaluation of the facts. In instances in which a diagnosis may be considered as creating a derogatory impression about a family, or of casting a shameful reflection on their good name, there might be a tendency not to think about a diagnosis which is unacceptable. Among the lower classes, or with more primitive patients, it is more acceptable to make a diagnosis of venereal disease. Psychiatric disabilities may be masked by cosmetic statements, and such incorrect diagnostic terminology as "nervous breakdown.' The obscuring of symptoms which might lead to a correct but "disgraceful" diagnosis is common on the part of the family and the patient. The doctor may be tempted to go along.

Diagnostic Dishonesty:

Social factors which lead to frank diagnostic dishonesty at least deserve some mention. Insurance payments which are withheld for certain diseases may prompt the family physician not to find such diseases. The industrial physician sees the patient as uninjured; but the patient and his physician or consultant may diagnose a disease produced by the trauma of the industrial accident. Diagnostic distortions of this type also contain elements of unconscious need to support a certain diagnostic appraisal. The frank and volitional distortions may take place for whatever real or rationalized motive the patient and physician might have. Diagnostic gyrations such as these, fortunately have a rather insignificant part in the total problem of diagnosis, and in the concepts and philosophy used for development of the diagnostic and differential diagnostic evaluation of a patient. Diagnostic dishonesty by the family may lead to confusion about a patient's illness when certain diseases of a chronic or disabling nature are present in the family of bride or groom. The chronically ill person may become involved in a conspiracy to conceal a diagnosis in order to enhance the possibility of a marriage proposal. Diagnostic dishonesty in job seeking may likewise lead to obscuring the diagnostic evaluation of an illness prior to employment, but which may flare up in an exacerbated form at a later date. A patient being treated for a neurotic disability revealed that his wife died suddenly of decompensated rheumatic heart disease only a few years after marriage. It became obvious as details developed that the family of the bride had gone to considerable lengths to obscure the history and presence of rheumatic heart disease at the time of marriage. The internist at that time was puzzled and questioned his diagnosis because of the complete absence of any history of previous rheumatic heart disease.

Diagnostic Fads and the Therapeutic Test:

Although the mature physician is well aware of the existence of fads in medical diagnosis, the medical student unfortunately tends to accept rather uncritically, inferences from facts which are alleged to justify certain currently popular diagnostic conclusions. A more critical evaluation would be healthier for his future practice of medicine. Especially are diagnostic distortions likely to occur when from vague and indefinite symptoms are derived a popularized diagnosis for the disability. Certainly the concept of "focal infection" with the extraction of teeth by the barrel full, and the removal of tonsils on a wholesale family basis is not as popular today as it used to be. The incidence of disease due to "focal infection" as a diagnostic entity has had a spectacular decline.

A somewhat related problem is one in which validity may be accorded a diagnosis because of the favorable response of the patient to treatment. This so-called "therapeutic test" for diagnostic purposes, although occasionally very valuable, tends generally to obscure, more often than cure. Recently Findlay in the

Clinics of North America described Trousseau as admonishing us to use new drugs while they still possess power to heal. "Enthusiasm and therapeutic results run hand in hand, as witness the current conflicting experiences with rice diet for hypertension." Even with definitely determined structural pathology, it has been shown that symptomatic relief is obtained in a very large percentage of patients when placebos are used. The therapeutic test of prostigmine given to a patient complaining of fatigue may confuse the physician into making a diagnosis of myasthenia gravis because of the dramatic response. Severe fatigue and muscle weakness on a neurotic basis may also respond dramatically to the prostigmine test thus demonstrating that a favorable therapeutic test result cannot be taken as proof of a diagnosis with certainty.

Diagnosis and Laboratory Workup:

With the increasing emphasis on laboratory methods and more elaborate and complicated procedures for studying biochemical alterations in disease, a word of warning must be sounded. Laboratory examinations offer many possibilities for the physician to avoid the strenuous time consuming work of talking with the patient, and with the patient's family, to find more and more facts, to think about them, and to evaluate them. Like other humans the physician seeks a way to make his task easier. The laboratory offers a ready opportunity to shunt off onto the chemical evaluations and his colleague in pathology, the necessity for dealing with frustrating circumstances or with resistance to his practice. Every patient who refuses to be thoughtful enough to have just the right symptoms and signs for an easy diagnosis, creates a potential situation in which laboratory findings may determine the course of the diagnosis.

Laboratory procedures are sometimes used by the physician as if technicians are by nature completely free from error, or that minor variations from a generally accepted norm are never to be expected within healthy limits. A slight variation may be given unusual emphasis if it fits in with the need of the doctor to make a certain diagnosis. Or it may be completely ignored as not significant if he refuses to have a finding interfere with a preconceived diagnosis.

How complete is a complete laboratory study? How far should laboratory findings be elaborated upon by further laboratory studies? Unfortunately it is so much easier to order laboratory studies and so much more difficult to spend time on a case and make further inquiries into the life of the patient and his family. It is generally held that a diagnosis cannot be made on the basis of laboratory data alone. The dictum to use laboratory procedures as a tool and not as a basis for final judgment is too often overlooked because the interviewing and examination process which might give more helpful information is so much more difficult and time consuming. We must constantly be on the alert to avoid seeking in laboratory procedures a substitute for the thought processes required of a physician. To avoid frustration is human, but errors in diagnosis are likely to be compounded by an indiscriminate use of the laboratory and a diminished use of what are probably the most valuable tools for medical diagnosis, the interview and the examination.

An aspect of "What's the Diagnosis?" which is seldom discussed is the process of converting a suspected but dubious diagnosis into a final diagnostic conclusion. A single laboratory finding just above the highest level for normal may be used as justification. For example, a diagnosis of hyperparathyroidism, leading to parathyroid surgery, may be justified on the basis of a single Ca level slightly above normal, despite a normal blood P. With large stones in the kidneys and hematuria responsible for the hospitalization, there seemed to be need for a more spectacular diagnosis to explain the stones. Parathyroid surgery, and the removal of a gland found to be normal on pathologic examination failed to dim the hope for a diagnosis of the more obscure and unusual disease.

As previously stated, the diagnosis may frequently be determined by the need of the physician to earn acclaim and recognition for finding the unusual. The mere

suspicion of an unusual disease may lead to a determined search for verification which is really not justified by the accumulating facts. The search for the rare disease often suggests the situation of the research worker who, having developed a hypothesis which is to be proven, continuously tries to do so but finds himself constantly uncovering facts which fail to substantiate the original impression. Or a less delicate analogy is the man who places a bet on the "long shot" and then proceeds to place more money on the same horse as his "long shot" goes into the final stretch three lengths behind the next to the last horse. The tendency to engage in such unusual diagnostic pursuits may be fostered by fads of medical diagnosis, or the recent brilliant diagnosis of a colleague which stirs up a competitive need to match or surpass. Our chagrin at having been caught short fosters the tendency to pursue laboratory data and to order more tests because we might fail again. Recently an intern suggested a Regitin test on a patient with a long standing hypertensive history. No history of marked fluctuations in blood pressure had occurred, no acute symptomatology commonly associated with pheochromocytoma was noted and the intern was aware of the fact that a competent internist had been treating the man for essential hypertension over many years. Puzzled at the interne's insistence on the importance of "ruling out pheochromocytoma" he was questioned further. It was revealed that only recently he had made a diagnosis of essential hypertension in a patient only to find to his dismay that the resident considered the possibility of a pheochromocytoma and that this suspicion was further verified by very definite findings on the Regitin test. It was quite obvious how this experience influenced his approach to the diagnosis of the hypertensive patient.

Telling the Patient the Diagnosis:

There are no formulae by which we may definitely be guided to serve as landmarks on what to tell the patient about a diagnosis. When a definite indication of appendicitis exists, and the need for surgical intervention is clear, the physician has no problem in communicating the diagnostic conclusion to the patient with the recommended treatment. When the diagnostic conclusion can be made as a positive statement with an accompanying hopeful prognosis and effective treatment, there is no cause for concern and philosophizing. As a general principle one is always involved in differential diagnostic deliberations about a patient, but the communication of such deliberations to the patient is highly undesirable. It has not been an unusual experience for me to see a patient who might have complained of headaches or dizziness or paresthesias to find that he had been told, "I didn't find anything wrong with you, but this could have been caused by a blood clot in the brain, or brain tumor, or a hardening of the blood vessels of the brain." It has always been my contention that no diagnosis is final and that continuously active differential diagnostic deliberations are a necessary part of the doctor-patient relationship. These deliberations should, however, be confined within the doctor's cranial cavity and should seldom be considered as appropriate communications to an already harassed patient. "Should the patient be told the truth about a serious illness?" is a question for unending discussion. The conveying of medical information concerning serious illness can not be standardized. It will vary with the physician, the patient, and the illness. There is a tendency for the physician not to tell patients about serious disease. Telling hypertensive patients their blood pressure is unwise, yet confidence in the physician is a most important element in stabilizing the ill patient. Failure to tell the truth may jeopardize this relationship. The patient with a progressive and fatal disease seems to be managed with a wide divergence of opinion. Many feel he should be told, others are fearful of precipitating depression, despair or suicide. In a recent interdisciplinary panel discussion at the Cornell Medical Center,[8] the psychiatrist, lawyer and minister of the panel felt that a patient diagnosed as having a fatal disease should be so told.

Some legal facts are worth keeping in mind. If one makes a statement to an-

other which is false, and he knows it to be false and there exists the intent to deceive, and if the recipient of the false information acts on that statement and is damaged thereby, he has the right to recover damages from the source of the false statement. Also there is no moral or legal principle that a doctor may invoke, with impunity, no matter how high his motives, to justify an untruth. Karlinsky[9] of the Winnipeg clinic expressed the desirable attitude as one of being neither alarming or overly sanguine. "He tells some what what he knows and what he does not know. He relieves anxiety with reassurance; he replaces fear with quiet understanding. He clears the air out, does not darken the horizon. He creates hopes out of despair."

Diagnosis by Exclusion:

Diagnosis by exclusion is a most common procedure in reaching a final diagnosis of a functional disorder. "I've ruled out everything and have done a complete workup. It must be functional." This is a distinctly negative approach. Making a diagnosis of emotional illness in a positive way depends primarily on an appropriate evaluation of three determinants: (a) the emotional illness, (b) the sychronization of onset, increase or decrease in symptoms with environmental stress or changes in the patient's adaptive techniques, and (c) the influence of any coexisting or contributory conditions such as organic illness. The physician's ability to make a positive diagnosis depends, therefore, on his skill in taking a medical history which gives proper emphasis to emotional factors, and on his familiarity with psychopathology.[10]

Again it must be emphasized that psychological disturbances are so commonplace that one must carefully evaluate complaints for evidence of structural alterations due to pathology caused by factors other than psychological. On the other hand structural pathology in middle aged and older persons is exceedingly common and some serious consideration must be given to the possibility that the psychopathology found is merely coincidental and not a cause of the patient's complaints. Diagnosis established by a single interview and "complete examination" is frequently followed by a pursuit of evidence to include or exclude something. In many cases this means the completion of the "laboratory workup." Little emphasis is placed on the importance for accurate diagnosis of a continued contact with the patient on an interview basis, of constantly expanding the onset and course material, exploring the personality makeup of the patient, past illness, and responses to illness, the patient's family and socio-environmental situation. A contact of as little as five to fifteen minutes daily if along these personal lines can be very rewarding for producing material which will help with the diagnosis. The physician may fall into the routine of checking his later contacts with the patient along such lines as follows: "How are your bowels today?" "How many times did you go?" "Do you have any pain today?", etc. This kind of requestioning about the presenting complaint will be rarely as rewarding as questions directed at producing more information about the total situation prior to the illness, and an interest in his current concerns, anxieties, and distress.

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